Fourth Edition

McAlpine's MULTIPLE SCLEROSIS

ALASTAIR COMPSTON

Christian Confavreux
Hans Lassmann
Ian McDonald
David Miller
John Noseworthy
Kenneth Smith
Hartmut Wekerle

CHURCHILL LIVINGSTONE

CHURCHILL
LIVINGSTONE
ELSEVIER

First published December 2005

First edition 1985
Second edition 1992
Third edition 1998

ISBN 044307271X

EAN 9780443072710

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of Congress

Notice
Medical knowledge is constantly changing. Standard safety precautions must be followed but, as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the Publisher nor the author assumes any liability for any injury and/or damage to persons or property arising from this publication.

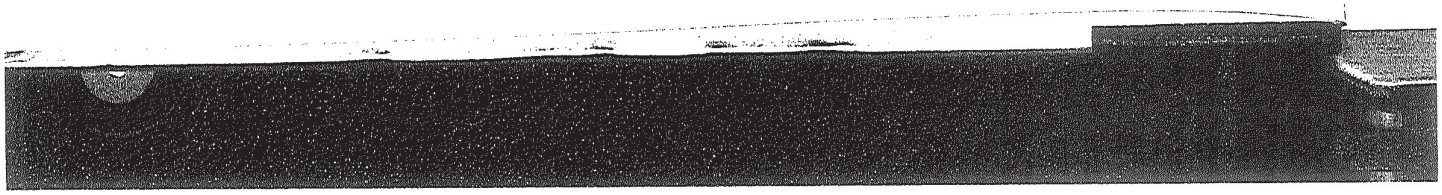
The Publisher

Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

For NDC (1918–1986)

Portrait by Howard Morgan. Reproduced by permission of Harveian Librarian, Royal College of Physicians of London.

Commissioning Editor: Susan Pioli
Project Development Manager: Louise Cook
Project Managers: Cheryl Brant (Elsevier), Gillian Whytock (Prepress Projects)
Editorial Assistant: Nani Clansey
Design Manager: Jayne Jones
Illustration Manager: Mick Ruddy
Illustrators: Antbits Illustration
Marketing Manager: Dana Butler



McAlpine's MULTIPLE SCLEROSIS

FOURTH EDITION

Alastair Compston PhD FRCP FMedSci
Professor of Neurology, University of Cambridge, Cambridge, UK

Christian Confavreux MD
Professor of Neurology, Hôpital Neurologique, Hospices Civils de Lyon and Université Claude Bernard, Lyon, France

Hans Lassmann MD
Professor of Neuroimmunology, Center for Brain Research, Medical University of Vienna, Vienna, Austria

Ian McDonald PhD FRCP FMedSci
Professor Emeritus of Clinical Neurology, Institute of Neurology, University College London, London, UK

David Miller MD FRCP FRACP
Professor of Clinical Neurology, Institute of Neurology, University College London, and Consultant Neurologist, National Hospital for Neurology and Neurosurgery, London, UK

John Noseworthy MD FRCPC
Professor and Chair, Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN, USA

Kenneth Smith PhD
Professor of Neurophysiology and Head of Neuroinflammation Group, King's College London School of Medicine at Guy's, London, UK

Hartmut Wekerle MD
Professor and Director, Max Planck Institute of Neurobiology, Planegg-Martinsried, Germany

Contents

18 Disease-modifying treatments in multiple sclerosis

John Noseworthy, David Miller and Alastair Compston

THE AIMS OF DISEASE-MODIFYING TREATMENT

There have been many developments since we last reviewed the role of disease-modifying treatments in multiple sclerosis. Collectively, these represent progress but fall well short of a solution to the problem. Results of the pivotal interferon and glatiramer acetate trials led to approval of these treatments by licensing bodies throughout the world. For the first time, patients with multiple sclerosis had a treatment. This was welcome and fuelled further efforts to improve on the evidence for efficacy and indications for the timing, dose and duration of therapy. Increasingly sensitive diagnostic criteria, bolstered by serial magnetic resonance imaging (MRI) studies (W.I. McDonald *et al* 2001), now allow more rapid diagnosis and hence – in our current climate – earlier exposure to treatment. However, further work is needed on many strategic issues and points of detail:

- Will early treatment make a difference?
- Can sensitive clinical and MRI measures detect early favourable trends that predict long-term benefit?
- Might the trials be made even shorter?
- How early in any study should a monitoring committee conclude with certainty that a trial is positive and recommend early termination with generalized access to the therapy?

It is axiomatic that doctors want to make their patients better. Patients want to lead normal lives unencumbered by any physical, psychological or life-style baggage related to multiple sclerosis. As clinical scientists, we need to structure that pastoral position around concepts of the pathogenesis and strategies for what realistically can be achieved. Patients with multiple sclerosis need treatment before the onset of fixed disability. Throughout, we have argued that the clinical manifestations of multiple sclerosis can be attributed to perivascular inflammation and the tissue injury with which it is inextricably linked. Since we last reviewed the subject in 1998, the diversity of mechanisms that injure nerve fibres throughout the illness and the contribution these processes make to the clinical course have been intensively studied. Concepts have been updated and revised. Thus, whilst we remain of the view that inflammation is pivotal to the destruction in parallel of axons and oligodendroglia, the inflammatory process also triggers biological processes that increasingly contribute to tissue destruction. What position should the prescribing physician take on how and when to treat the person with multiple sclerosis? Our stance is pragmatic but informed by the neurobiology and neuroimmunology, and by the evidence from clinical trials.

We structure this discussion around the formulation that, typically, the early clinical course of multiple sclerosis is marked by relapses from which symptomatic recovery is usually complete. Inflammation drives the process. Subsequent episodes may affect the same or different myelinated pathways. Before long, clinical deficits, which correlate with abnormalities in saltatory conduction of the nerve impulse, accumulate. These reflect loss of functional reserve in the adaptive capacity of the nervous system to make best use of surviving electrical activity, and the impoverished but detectable signals that reach the cortex or distant parts of major pathways. Then, inflammation wanes (without necessarily ceasing) and the relative contribution of cumulative axonal damage, amplified by loss of trophic support, makes an impact (Figure 18.1). Initially, the clinical course is intermittent in 80% of affected individuals but a high proportion do later enter the secondary progressive phase in which impairment, loss of ability, and impact on health-related quality of life are each affected. For these patients, disability is established in 40% by 10 years, in 60% by 15 years and in 80% (that is 50% of all patients) by 25 years. It is the onset of secondary progression that gives multiple sclerosis the frightening reputation it has amongst affected individuals. Progression is the main factor distinguishing mild from severe forms of multiple sclerosis. In 20% of patients, the disease progresses slowly from onset, most typically with predominant spinal involvement, and this form of multiple sclerosis is even more predictably disabling. The analysis that fully reversible deficits mainly result from inflammtion, oedema and the physiological action of cytokines whereas persistent symptoms and signs can be attributed to demyelination and the initial wave of axonal damage with failure of recovery mechanisms, and that chronic progression is attributable to cumulative axon degeneration, has obvious implications for treatment.

Immunological therapies are most likely to be effective in the inflammatory (relapsing–remitting and relapsing–persistent) phases. Conversely, it will be more difficult to influence progression with immunotherapy. Any treatment that reduces the accumulation of disability, and inhibits or delays time to onset of the progressive phase, is most likely to have a clinically useful disease-modifying effect whether or not that treatment also

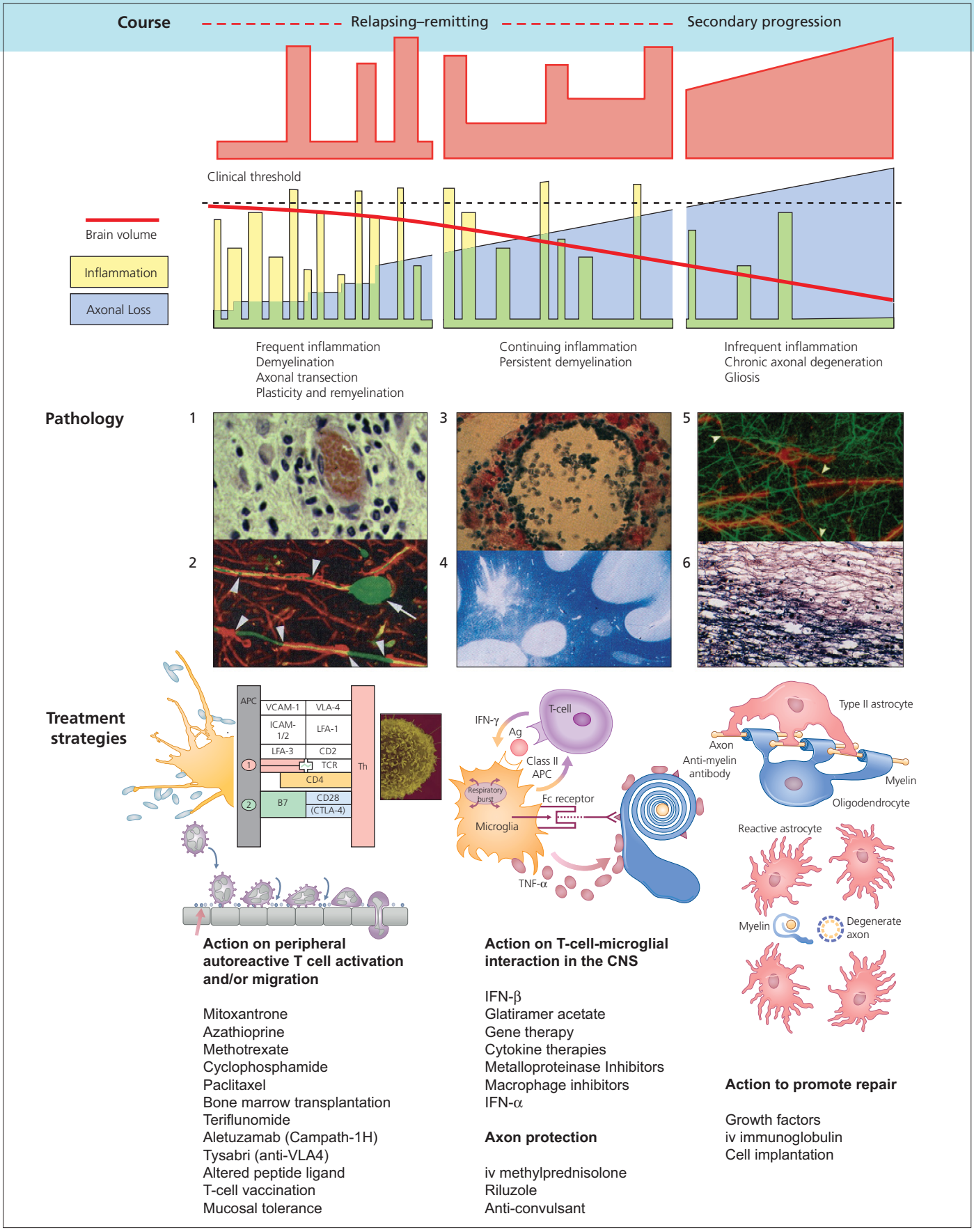


Figure 18.1 The course, pathogenesis and treatment of multiple sclerosis. *Course*: the clinical phases of relapse with recovery, relapse with persistent deficits and progression depend mainly on the effect of inflammation, demyelination and axon degeneration, respectively. Disease activity is often presymptomatic and, later, not invariably expressed clinically. As inflammation wanes, brain volume reduces with accumulated axonal loss. *Pathology*: perivascular inflammation (panel 1) causes acute axonal transection (panel 2), and microglia-mediated removal of myelin (panel 3) with persistent demyelination despite some remyelination (panel 4); chronic lesions show further axonal loss (panel 5) and gliosis (panel 6). The scheme does not depict primary progressive multiple sclerosis in which there is significant axonal degeneration with or without a preceding inflammatory phase. *Treatment strategies*: target the phase of T-cell activation in the periphery or cell migration; interactions between the activated T cell and microglia in the central nervous system; and axon protection and remyelination. Adapted from Compston and Coles (2003). © 2003, with permission from Elsevier.

affects the number of new episodes or lesions detected by brain imaging. Therefore, it makes sense to deploy strategies for treatment that address this evolution of events – choosing those interventions that preferentially tackle (or, preferably, anticipate) the individual components so as to be maximially effective. Although much contemporary research in multiple sclerosis is appropriately directed at identifying disease-modifying treatments, many patients already make clear that merely aspiring to shape the future course of the disease is not sufficient. They want to get better. If repair is a matter of restoring structure and function, it follows that dealing with the rewriting of neurological history requires treatments that enhance plasticity and reconstruct the myelinated axon in its network of connectivity. Thus, repair involves applying the lessons of neurobiology to the problems of multiple sclerosis. It remains possible that enhanced remyelination will occur in an immunologically stable environment. The experimental evidence already hints at this possibility (see Chapter 10). Remyelination may protect injured axons from further damage resulting from loss of trophic support. Conversely, optimizing their growth factor environment may reduce the extent to which axons, already insulted, are affected by further exposure to inflammatory mediators. Conversely, it is logical to assume that sophisticated repair strategies will have a low dividend for success without first having available a treatment that reliably stabilizes the disease process. Just as the dichotomy of genes versus environment is a somewhat sterile aetiological debate, so too separating inflammatory and biological mechanisms of injury to the axon–glial unit is somewhat strained.

But to go back a step, in Chapter 1 we reviewed the development of ideas concerning disease-modifying treatments in multiple sclerosis. The era prior to 1980, summarized by W.I. McDonald (1983), was empirical and largely uncluttered by serious concern about disease mechanisms. This period of intellectual freedom concerning the nature of multiple sclerosis provided ample opportunity for wild, and at times frivolous, approaches to treatment, some of which (rightly) gave the disease the bad therapeutic name from which it has not yet fully recovered. An important development in the treatment of multiple sclerosis in the 1980s was the acceptance that therapeutic claims must adopt orthodox clinical trial methodology based on blinding (single or double), use of controls (preferably placebo but sometimes receiving best existing medical practice), matching groups at entry for potentially confounding variables, setting primary outcome measures at the outset of the study and not trawling for the best result on completion, and considering power calculations during the planning stage. Working groups were convened to issue guidelines (see, for example, J.R. Brown *et al* 1979; Weiss and Dambrosia 1983). The impact of papers laboriously listing trial design tactics encouraged journal editors and referees to flex their methodological muscles – factors which undoubtedly led therapists to conform and resulted in the steady demise of therapeutic generalizations based on anecdote. The rubric 'double-blind, randomized and placebo-controlled' became commonplace. Since progress in identifying useful treatments was disappointingly slow, through no fault of those who designed the studies, separate trials of many agents proliferated and none could be regarded as definitive. Patients violated protocols and left studies for open label treatments, making it necessary to sort those who completed studies from 'intention to treat' cohorts. Commentators struggled to put their thoughts in order by cataloguing published material and seeking a best position on disparate data. Faced with too few studies involving sufficient numbers of patients from which to draw firm conclusions, the meta-analysis emerged as a device for 'seeing the wood for the trees'. Considered by some as scientific sophistry, this analytical procedure exposed the criticism of mixing chalk with cheese and creating statistical noise, not least because outcome measures in multiple sclerosis are an integral of up to three independent clinical features – acute events, persistent deficits, and progression – which contribute to impairment, loss of ability, autonomy and participation (formerly referred to as impairment, disability and handicap).

Later, came the interim analysis – often used to stop trials either on the grounds of futility or issues of patient safety. Recent examples include studies of intravenous immunoglobulin designed to measure clinical recovery in multiple sclerosis and optic neuritis; trials of altered peptide ligands; the story of agents that have an impact on tumour necrosis factor-α (TNF-α); the glatiramer acetate study in primary progressive multiple sclerosis; and the use of oral glatiramer acetate (see below for more detailed discussion). However, the interim analysis has also recently been used increasingly to stop trials early on the basis of perceived efficacy, thereby allowing active treatment to be made immediately available for all patients without the disadvantaged controls waiting for completion of the protocol. We have seen this happen repeatedly, dating from the first wave of pivotal trials in relapsing–remitting multiple sclerosis [the North American IFNβ-1a trial (Avonex)] and, subsequently, with trials in possible (CHAMPS) and secondary progressive multiple sclerosis (the European trial, SPECTRIMS) – all discussed below. More recently, trials have been reported and widely accepted as valid with as little as 6 months follow-up (for example, EVIDENCE). The lesson from the failed Mayo Clinic Canadian Sulfasalazine Trial that early benefit may wane with further blinded follow-up seems often to have been forgotten (Noseworthy *et al* 1998; Rudge 1999). Hence, we now have to provide wise counsel to a generation of patients, some treated immediately after an inaugural clinical episode (clinically isolated syndromes), others when the illness has been established for only a few years (early relapsing–remitting multiple sclerosis), and many long into the illness with advanced secondary progressive disease – despite the lack of convincing evidence for protracted benefit – aiming to steer a course between managing their expectations and not shirking our responsibilities as clinical scientists.

The concentration of clinical research on the evaluation of therapies that target the immune response in multiple sclerosis itself represents something of an advance, displacing hypotheses for the pathogenesis finding their expression in less rational clinical trials. We hope that those who contributed to these studies will accept our decision to concentrate on contemporary immunotherapy and applied neurobiology. Of course, we accept that some (or indeed many) of the agents which we have selected for detailed discussion may in time join those which we have placed on the well-stacked shelves of therapeutic history in multiple sclerosis.

By the late 1980s, Noseworthy *et al* (1989b) were able to tabulate a large number of potential therapies which experienced investigators considered to be promising options for treatment. Many are still being evaluated but some degree of consensus on

the basis for treatment in multiple sclerosis has emerged in recent years. At first, physicians were cautious when considering the use of immunotherapy for multiple sclerosis even though many of the available medications had been used successfully in other inflammatory and autoimmune diseases. This caution was appropriate since a significant proportion of affected individuals remain free from disability despite having intermittent symptoms over several decades, and it is not possible to segregate individuals destined to have benign forms of multiple sclerosis early in the course. In our opinion, however, the focus on treating secondary progressive multiple sclerosis held up progress for a generation. Since the late 1990s, that lesson has been clear. Wait until late and the contribution of anti-inflammatory therapy is so small as to not be cost effective. For many affected individuals, this is a formula for disappointment leading to cynicism that, despite intense research, no useful progress is being made in understanding the disease. It seems clear that, in the context of disease progression, the focus should now be on neuroprotective and biologically motivated approaches – alone or in combination with immunotherapy. Treat early and the dividend may be greater but still the dilemma remains. Drugs that are partially effective may not sufficiently stabilize the disease processes whereas the more actively anti-inflammatories are likely to carry nontrivial adverse-effect profiles. As we wrote in the early 1990s, the comprehensive management of multiple sclerosis is about both limiting and repairing the damage.

Progress has been made in improving outcome measures in the assessment of treatments for multiple sclerosis. Totting up the number of acute events requires them to be reliably defined, but patients will understandably assign significance to transient alterations in symptoms, perhaps having explanations other than disease activity. Conversely, motivation and the hope of a therapeutic effect will lead others to ignore clinical changes even though these are biologically meaningful. Periods of disease activity measured by high relapse rates tend to oscillate and, overall, slow with time so that a reduction in relapse rate *per se* is not necessarily impressive unless the placebo group has behaved less well and in keeping with the known natural history of the disease. The problems are even greater for the assessment of disability. There have probably been more critiques of the Expanded Disability Status Scale of Kurtzke (EDSS) (Kurtzke 1983a)and related clinical outcome measures than clinical trials in multiple sclerosis. The problems are well known. The EDSS mixes activity with disability and ignores participation. It is excessively weighted towards the motor system. It is ordinal not linear. Patients tend to cluster in the lower and higher echelons and it is insensitive in the middle range. However, it survives and despite much squabbling has yet to be replaced by a better, fully validated and universally accepted system. In this context, we welcome the deliberations of a panel convened by the United States National Multiple Sclerosis Society to make recommendations for a comprehensive clinical outcome system applied universally to treatment trials in multiple sclerosis, so allowing more meaningful comparisons between studies of the same or different agents (Rudick *et al* 1996a). The original guidelines were subsequently updated with special emphasis on the need for advisory/steering (to comment on the rationale, design, protocol, accrual and ownership of the data) and safety committees (to monitor operational aspects of trials), and the involvement of a group to supervise publication (Lublin *et al* 1997). The panel derived the Multiple Sclerosis Functional Composite scale (MSFC; G.R. Cutter *et al* 1999; Rudick *et al* 1996a; 1997) specifically to resolve these matters. The MSFC integrates scores on a timed 25 foot (7.5 m) walk (T25FW), Nine-Hole Peg Test (9HPT) of upper limb function, and Paced Auditory Serial Addition Test (PASAT). Values are reported as a Z-score, derived from comparison with an index population from the National Multiple Sclerosis Society Task Force dataset (G.R. Cutter *et* al 1999). The scale awaits validation as an accepted outcome for clinical trials and the MSFC has yet to be embraced by practising and academic neurologists. In large part, this is because, using this metric, most do not understand what is meant by changes in the Z-score, whereas few have difficulty with a single or multiple step change in the EDSS.

The introduction of novel scales has been trivial by comparison with the introduction of surrogate MRI markers as indices of therapeutic efficacy. The apparently favourable impact of approved but, in the event, partially effective treatments on relapse rates and MRI appearance solidified the sense that trials could increasingly use surrogate markers to detect a treatment effect. Clearly, reduction in the initial frequency of relapse and MRI activity may genuinely predict prolonged benefit but this requires evidence and has yet to be demonstrated. Such a study design aims to push new and existing therapies over a very high hurdle, requiring huge investments of time and money. Only recently have investigator-led studies adopted this long-term view but attention to effects that last and shape the neurological future is in the interests of patients and should be seen as motivated by the highest principles of clinical science, with a real dividend for improvement from the investment of hope in treatment. Worried by the sustained use of imperfect instruments for assessing outcome, investigators have created and partially validated increasingly sensitive measures of disability (such as the MSFC) and shown that these may detect treatment differences between treated patients with secondary progressive multiple sclerosis and controls, when standard measures (the Kurtzke EDSS) do not. Is the problem that our measures of disease progression are too insensitive to recognize a favourable response to treatment? Rather, it seems increasingly likely that existing treatments are insufficiently effective, or are deployed too late, completely to inhibit advancing disability.

The essential yet daunting task of confirming that these sensitive measures matter clinically in the long term – and are thereby predictive of a meaningful long-term benefit – has yet to be established. Here, a difference in agenda exists between physicians and the pharmaceutical industry, spawning secondary tensions between doctor and patient. The clinical scientist has a responsibility to proselytize secure knowledge even if this is gathered slowly and is disappointing in its scope. Sponsors need an early return on investment. In the context of multiple sclerosis, *Big Pharma* can be caricatured as having avoided engaging investigators in a dialogue about the importance of establishing long-term disability benefits. In turn, licensing agencies have not required that industry, assisted by teams of clinical investigators, demonstrate continued benefit for these expensive drugs as the necessary qualification for a drug licence. We have seen a proliferation of extension trials designed to demonstrate continued benefit. However, as discussed below, most are degraded by bias resulting from the recurring reality that failing patients drop out at the completion of the proper trial. Conversely, responders are

better motivated to participate in the extension limb of the study. Although re-randomized, loss of the original 'treatment failures' introduces selective sampling that subsequently haunts the trial, thereby reducing confidence that any long-term benefit claims are real. The push to earlier treatment, and acceptance by patients and physicians of the need for prolonged use of the currently available drugs (even in the face of obvious ongoing disease activity dressed up around 'perhaps the treatments are helping a bit'), is bolstered by several factors. Sponsors of the approved agents have failed to press for clinical and laboratory biomarkers that characterize responder status. As a result, far more patients are being treated than might be appropriate given the partial benefits noted in the literature.

These recent changes in the attitudes of specialists in multiple sclerosis should not be seen as mulish obstruction to the pharmaceutical agenda. Investigators and sponsors share the sense of urgency in wanting to provide patients with effective drugs as soon as possible. More than $1 billion is spent annually on these agents, in the United States alone, with no funds invested to confirm sustained benefit. This hope that treatment with existing agents will provide an extended benefit, especially for patients treated early, remains just that – an unconfirmed, elusive concept without proof for patients and physicians. Meanwhile, little (if any) progress is being seen in creating a robust strategy to validate this goal. If we appear critical, it is in the spirit of prioritizing real not virtual progress. Our attitude is in the interests of people with multiple sclerosis and the advancement of clinical science, with personal reputation and commerce well down the motivation stakes.

THE PRINCIPLES OF EVIDENCE-BASED PRESCRIBING IN MULTIPLE SCLEROSIS

As discussed in the preceding section, over the last decade clinical investigators have become increasingly familiar with the principles of clinical trial design and have adopted these structures in the evaluation of putative new treatments. Thus, practice has shifted from the extrapolation of anecdotal experience to a more evidence-based stance on prescribing (Sackett *et al* 2000). The concepts of levels of evidence and grades of recommendation are slowly becoming part of the clinical trials lexicon. The neurological community is increasingly demanding that published reports of clinical trials clearly state how each trial was conducted and wishes to know how the data were analysed and by whom. Prior to 1994 it was common to see trials that were neither randomized, blinded, nor adequately controlled. Patients with different disease courses (relapsing–remitting, and primary or secondary progressive) were often included in the same study; this latter concern is still rarely addressed. At that time, trials rarely performed an intention to treat analysis, often accounted incompletely for drop-outs, and rarely assessed the adequacy of efforts to blind patients and evaluators. Outcome measures were usually not validated (regrettably, this is still largely the case). Nor were the sensitivity and specificity of these measures provided in the reports. Sample size estimates and power calculations were often not stated, leaving open the possibility of type 2 ('false-negative') errors resulting from an underpowered sample size. Many authors did not state the predetermined primary outcome measure and post-hoc analyses were often not identified as such. Authors rarely corrected for multiple statistical comparisons (the Bonferroni correction).

With time, the clinical trials community in multiple sclerosis has become increasingly sophisticated about these essentials of trial design and conduct. Most of the design flaws already listed are now appropriately filtered during design of the protocol, and policed by the peer review process before a report is published. However, some problems remain. As emphasized repeatedly throughout this chapter, clinical trials in multiple sclerosis are rarely of sufficient duration to determine whether the intervention affects eventual outcome in terms of disability but there are many seemingly insurmountable obstacles that block the path to longer trials. These include the lack of 'equipoise' for selecting both the active treatment(s) and the control group, since many investigators have strong opinions about which treatments they consider to be superior. There is reticence by both the sponsor and patients to commit to long trials. To date, every treatment has proved incompletely effective and this regrettable truism results in an inevitable but variable degree of 'treatment failure' for most participants – most patients experiencing clinical or MRI evidence for worsening. Naturally, the disappointed patients who detect clinical worsening remain anxious to try another form of treatment and many options are now available. Whitaker (1993), on behalf of the Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis of the National Multiple Sclerosis Society (NMSS), argued against named patient prescribing (compassionate use of investigational drugs) since this bypasses or otherwise compromises the double-blind, randomized and placebo-controlled trial. His views are no less relevant today when patients have been given high expectations of drug treatment and efficacy has been proselytized through a combination of altruism and exploitation. Many doctor–patient relationships have been strained by these helter-skelter events. Agreement on trial design and protocol management and policing of methodology in treatment trials continues into the new millennium. With increasing duration, drop-outs accumulate and blinding of the patient and evaluator become increasingly difficult. Similarly, as discussed later in this chapter, extension trials are flawed by the late loss of protection from the initial randomization step that is so essential to reduce bias by balancing unknowable prognostic variables across each study group. Most reports of positive trials do not discuss the 'numbers needed to treat' analysis (see below), although independent editorials and correspondents frequently raise this matter; there remains a pressing need to establish that MRI measures can serve as reliable predictive biomarkers of disease course.

It is regrettable to acknowledge that few investigators participating in industry-sponsored trials yet have full access to raw data or the process of analysis. This continues to be a vexing problem in multiple sclerosis research despite requirement by major clinical journals for authors to confirm that an opportunity was provided to participate both in the collection of results and their analysis (Davidoff *et al* 2001). The academic community is gradually accepting the importance of so-called integrity policies that mandate full disclosure of competing interests with sponsors but greater transparency on this issue is still needed (Noseworthy *et al* 2003). The strong stance taken recently by major biomedical journals to require that trials be fully registered, if they are to be accepted for publication, may provide

much needed clarity within the clinical trials arena (De Angelis *et al* 2005).

With the proliferation of partially effective, disease-modifying treatments, fewer untreated patients are available to participate in clinical trials. In 1998, a small group of investigators decided to create a research centre independent of commercial influence and with the goal of hastening the search for therapeutic advances (Noseworthy *et al* 2003). The Sylvia Lawry Centre for Multiple Sclerosis Research at the Technical University of Munich (named in honour of the founder of the National Multiple Sclerosis Society of the United States and the International Multiple Sclerosis Society – see Chapter 1 – and directed by Albrecht Neiss and Martin Daumer) has amassed an impressive repository of data from natural history and completed clinical trials. In 2004, it had access to 43 data sets involving 14 700 cases and representing 62 000 patient years of follow-up. These data were primarily orientated towards controls since pharmaceutical sponsors had yet to donate information on individuals receiving study medications. Efforts are already under way to use this resource as the basis for understanding the contribution of demographic variables and laboratory measures (primarily MRI data) in identifying characteristic of the short- and long-term clinical course. The aim is to apply this knowledge in predicting the long-term course early in what is, for most affected individuals, almost invariably a chronic illness. Several countries (Denmark, Canada and Spain amongst others) have developed national registries to monitor the use of expensive therapies. Such databases will increasingly provide insights on long-term treatment efficacy with these drugs.

THE ROLE OF MAGNETIC RESONANCE IMAGING IN CLINICAL TRIALS

Over the last decade, the application of a range of MRI outcome measures has become a standard means of assessing therapeutic efficacy in the context of controlled clinical trials. The potential to monitor both natural history and treatment interventions was quickly recognized when MRI was introduced into clinical practice in the 1980s. As a direct and sensitive surrogate measure of the evolving disease process, it promised outcome measures that were simultaneously more objective and efficient than the cumbersome clinical markers on which clinical trials exclusively depended at that time. In the first clinical trial of interferon-β (IFN-β), culminating in a drug licence, the unequivocal evidence that new lesions could be prevented was seen as strong supporting evidence to accompany the principal clinical effect of a reduction in relapse rate (Paty *et al* 1993).

Individual magnetic resonance imaging lesions

The sensitivity of counting new MRI lesions in treatment monitoring has been amply confirmed. In relapsing–remitting or relapsing secondary progressive multiple sclerosis, serial monthly brain MRI reveals about ten new gadolinium enhancing or new T_2 lesions for every clinical relapse. It can thus be anticipated that the number of subjects and length of follow-up is reduced when using MRI lesions as the primary outcome measure (D.H. Miller *et al* 1991). Significant reduction in the number of new MRI lesions can be demonstrated in a matter of months using a relatively small number of patients and, as a result, MRI has been proposed – and is widely accepted – as the primary outcome measure in exploratory trials of potential new disease-modifying agents in relapsing multiple sclerosis (D.H. Miller *et al* 1996). This approach is biologically plausible when the treatment is intended to suppress inflammation, since gadolinium-DTPA (gadopentetate dimeglumine) enhancing lesions identify areas of active inflammation. Monthly T_2-weighted and gadolinium-DTPA enhanced (0.1 mmol/kg of a gadolinium chelate) brain MRI are usually performed in phase I/II studies. In relapsing–remitting multiple sclerosis, a parallel groups design with placebo requires about 40 patients per arm to show a 60% reduction in new enhancing lesions over 6 months (McFarland *et al* 1992; Sormani *et al* 1999; Tubridy *et al* 1998a). A single run-in scan at 1 month reduces the sample size by about 30% (Tubridy *et al* 1998a). Slightly larger numbers are needed in secondary progressive multiple sclerosis. Crossover designs are more powerful, because there is less intra- than inter-patient variability in MRI activity. A single crossover design with 6 months run-in followed by 6 months of treatment requires between 10 and 12 patients to show a 60% reduction in activity (McFarland *et al* 1992). Double crossover designs are even better, but there needs to be a wash-out period between the two phases. Both crossover designs are compromised by regression to the mean. If a safe and cheap drug shows only a moderate reduction in activity (c.50%) in a small crossover study, this might be sufficient evidence to justify going straight to a phase III trial using a clinical end point. However, if the drug has more side effects or is expensive, a parallel group design with the larger sample sizes (such as 2 groups of 40 individuals treated for 6 months) should first be undertaken to gain more certainty about the MRI effect. An important limitation of studies with this size and duration is that they will not detect infrequent, severe or delayed side effects. It is therefore still considered necessary for the definitive (phase III) trial to be longer, to involve larger cohorts and to have a primary clinical end point.

A major limitation in the interpretation of gadolinium enhancing or T_2 lesions as outcome measures in trials is that these do not strongly predict or correlate with the long-term clinical course. Although concordance of the treatment effect on MRI lesions and relapses has been observed with most (but not all) agents that have been investigated in placebo-controlled trials (Table 18.1), the magnitude of reduction on MRI has not reliably predicted the extent of any decrease in relapse rate. For example, IFN-β and glatiramer acetate both reduce relapse rate by about 30% but, whereas IFN-β reduces the new MRI lesion rate by 50–70%, glatiramer acetate is associated with only 30% reduction. More importantly, the extent of T_2 and gadolinium-DTPA enhancing lesions has consistently demonstrated little or no relationship with concurrent or future disability (Kappos *et al* 1999). This lack of a relationship may partly be the result of limited follow-up – most published studies have lasted no more than a few years and may not have allowed sufficient time for substantial changes in disability to be revealed. Two recently published cohorts of patients presenting with clinically isolated syndromes have been followed for 8.7 and 14 years, respectively. One study of 42 patients showed that infratentorial lesions at presentation are associated with greater disability after 8.7 years (Minneboo *et al* 2004). In the second, the number and

Table 18.1: Treatment effects on active MRI lesions and relapses reported in parallel groups, placebo-controlled multiple sclerosis treatment trials

Therapy	Sub-group	Treatment duration	Patient number	MRI effect %	Relapse effect %	Reference
Beta interferon 1b SC	RR	4 years	372	–60 to 75	–33	IFNB Study Group (1995)
Beta interferon 1a IM	RR	2 years	301	–50	–31	Jacobs *et al* (1996)
Beta interferon 1a SC	RR	2 years	560	–75	–27 to 33	PRISMS Study Group (1998)
Beta interferon 1b SC	SP	3 years	718	–65	–31	D.H. Miller *et al* (1999)
Beta interferon 1a IM	CIS	2 years	383	N/A	–44	Jacobs *et al* (2000)
Beta interferon 1a SC	CIS	2 years	308	–33	–23	Comi *et al* (2001)
Beta interferon 1a SC	SP	3 years	618	–73	–30	SPECTRIMS Study Group (2001)
Beta interferon 1a IM	SP	2 years	436	–46	–33	J.A. Cohen *et al* (2002)
Alpha interferon	RR	6 months	20	–95	None[a]	Durelli *et al* (1994)
Linomide	RR	6 months	31	–70	None[a]	Andersen *et al* (1996)
Linomide	SP	6 months	30	–55	None[a]	Karussis *et al* (1996)
Anti-CD4 antibody	RR/SP	6 months	71	None	–41	van Oosten *et al* (1996)
Mitoxantrone	RR/SP	6 months	42	–90	–77	Edan *et al* (1997)
Lenercept	RR	6 months	168	+30 to 60	+50 to 68	Lenercept MS Study Group (1999)
Tysabri	RR/SP	2 months	72	–50	None[a]	Tubridy *et al* (1999)
Cladribine	SP/PP	1 year	159	–80	None	G.P. Rice *et al* (2000)
Glatiramer acetate	RR	9 months	239	–29	–33	Comi *et al* (2001)
Mitoxantrone	RR/SP	2 years	194	–85	–60	Hartung *et al* (2002)
Oral beta interferon	RR	6 months	173	None	None	Polman *et al* (2003)
Tysabri	RR/SP	6 months	213	–90	–50	D.H. Miller *et al* (2003)

a Study too small to reliably evaluate relapses.
RR = relapsing–remitting; SP = secondary progressive; CIS = clinically isolated syndrome; PP = primary progressive.
– = decrease in activity rate treatment versus placebo.
+ = increase in activity rate treatment versus placebo.
SC = subcutaneous; IM = intramuscular.
N/A = not possible to assess because of patient censoring on developing clinically definite multiple sclerosis.

volume of T_2 lesions in 71 patients at presentation correlated modestly with EDSS after 14 years (Brex *et al* 2002). The increase in T_2 volume during the first 5 years correlated somewhat more strongly with disability at year 14 ($r = 0.61$), suggesting that early accumulation of an increased lesion load does partially relate to long-term outcome. These studies are, however, quite small and the strength of the relationship between lesions and disability remains modest, suggesting that it is not sufficient to rely on MRI lesions *per se* (or their modification by treatment) to predict long-term disability (or its prevention by treatment).

The poor predictive value for disability of T_2 and gadolinium-DTPA enhancing lesions is that they are neither specific nor sensitive to axonal loss – the major pathological substrate for irreversible disability in multiple sclerosis. These markers do not reflect axonal attrition within lesions, or the loss that occurs more widely in normal-appearing white and grey matter. As a result, increasing attention has been placed on surrogate MR measures of axonal loss to study disease progression in multiple sclerosis and its modification by treatment.

It has been suggested that axonal loss in MRI lesions may be inferred by the presence of T_1 hypointensity. Such lesions (colloquially described as T_1 black holes) account for 20–30% of all T_2 visible lesions and have been found in post-mortem studies to indicate a greater extent of axonal loss than lesions that remain T_1 hypointense (van Walderveen *et al* 1998b). However, the use of T_1 hypointense lesions as a surrogate marker for axonal loss has important limitations. First, not all such lesions are irreversible – acute enhancing lesions frequently display transient hypointensity, and their resolution with follow-up may simply imply that reversible mechanisms such as oedema contribute significantly to the appearance. Secondly, T_1 hypointensity is a subjective assessment that is less reproducible than T_2 lesion identification and is highly dependent on MR sequence parameters. Thirdly, T_1 hypointense lesions are almost never seen in the spinal cord, yet axonal loss in this location is crucially related to locomotor disability. Fourthly, being a subset of visible lesions, assessment of T_1 hypointensity provides no indication of the axonal loss occurring in normal-appearing tissues.

It has been useful in placebo-controlled clinical trials to follow the evolution of acute inflammatory gadolinium enhancing lesions through to areas of persistent T_1 hypointensity. The frequency of such an evolution is reduced in patients treated with glatiramer acetate compared to the placebo group (Filippi *et al*

2001a) and Tysabri (Dalton *et al* 2004a) but not IFN-β (Brex *et al* 2001b). This outcome could be considered as the MR equivalent of an incomplete recovery from relapses. However, given the abundant evidence for neuronal and axonal loss in the white matter and grey matter beyond MR visible lesions, attention is being focused on global MR measures as a more plausible surrogate marker of irreversible and progressive disability.

Global magnetic resonance measures of neuronal and axonal loss: atrophy

Tissue loss (atrophy) is the most widely used measure of neuroaxonal loss in treatment trials. Axons contribute 45% to white matter volume, followed by myelin (25%) and other tissue elements (glial and vascular tissues and water: D.H. Miller *et al* 2002). Neuronal cell bodies and axons constitute the bulk of grey matter volume although myelin is also present, albeit to a lesser extent than in white matter. Atrophy of white or grey matter in multiple sclerosis in large part reflects axonal and neuronal loss. In a study of the spinal cord of five people with multiple sclerosis, marked atrophy and axonal loss were both observed (Bjartmar *et al* 2000). However, neuroaxonal loss is not the only cause of atrophy. Loss of myelin, variations in glial bulk, inflammation and tissue water content also affect global or regional volume measures in multiple sclerosis. Pertinent to treatment trials, it should be noted that anti-inflammatory therapies (such as high-dose corticosteroids or IFN-β) reduce brain volume without axonal loss having occurred. We recommend that a period of 3 months should elapse after receiving such therapy before inferring that atrophy is measuring axonal loss.

The optimal technique for detecting atrophy should be reproducible, sensitive to change, accurate and pragmatic. The two distinct methodological aspects involved in measuring tissue volumes are data acquisition and data analysis. The ability to reduce partial volume errors with high resolution scans means that 3-D acquisitions are attractive, although 2-D sequences (Molyneux *et al* 2000) have also been used successfully to derive cerebral volume measures. Segmentation of the brain is necessary for whole brain atrophy measurements, and suppression of cerebrospinal fluid helps to generate a sharp distinction in signal between cerebral and extracerebral matter. The most widely used 3-D sequence is a T_1-weighted gradient echo. Specific study of white or grey matter requires good contrast at the cortical boundaries and interfaces both with cerebrospinal fluid and the individual lesions. It is aided by multiple contrast acquisitions (e.g. T_1, T_2 and proton density).

Manual outlining provides the simplest approach to measuring changes in volume and is useful in small structures or regions such as the third ventricle, where significant atrophy occurs in multiple sclerosis. Disadvantages of manual segmentation include operator bias, long analysis time and poor reproducibility when compared with automated techniques. Semi-automated methods improve speed and reproducibility. Regional segmentation algorithms are used to outline lesions, spinal cord, optic nerves and ventricles. Many automated methods exist for segmentation (and thus volume measurement) of the whole brain. Both single contrast (Chard *et al* 2002c) and multispectral data (Ge *et al* 2000) are utilized for whole brain segmentation. Usually, the difference in signal intensity between brain parenchyma and cerebrospinal fluid on a single contrast acquisition is enough to drive the segmentation process. Segmentation of grey and white matter may also be accomplished with either single contrast or multispectral data, although additional sophistication is required to separate the two tissue types. Methods include Statistical Parametric Mapping (SPM) based segmentation (Ashburner and Friston 2000) and the fuzzy C-means algorithm (Pham and Prince 2000). Masking of lesions is necessary to avoid misclassification.

Estimates of absolute volume at separate time points are not necessarily needed. Evidence for atrophy may be obtained by looking for differences between serial scans (S. Smith *et al* 2001). Nonlinear registration of such scans produces deformation fields that yield information concerning regional and global atrophy, and rigid body registration can be used to track displacement of the brain surface during atrophy (Freeborough and Fox 1997; 1998). Normalizing to head size reduces intersubject variations in brain volume. Relative volumes also remove variability due to scanner instability. The scalp, and the total intracranial capacity (determined by the sum of the volumes of grey matter, white matter and cerebrospinal fluid, or the sum of the brain and ventricular and sulcal cerebrospinal fluid) have all been used to adjust brain volumes for normalization. Atrophy is seen in both the brain and spinal cord in secondary and primary progressive multiple sclerosis. It is most marked in secondary progressive disease and correlates with disability (Kalkers *et al* 2001; Lin *et al* 2003; Losseff *et al* 1996b). In primary progressive multiple sclerosis, significant atrophy of brain and cord over 1 year was evident in a large cohort of primary progressive patients drawn from six European centres (Stevenson *et al* 2000). Change in cerebral volume over this period correlated only weakly with change in T_1 and T_2 brain load. More recently, progressive cerebral and cervical cord atrophy has been observed over a 5 year follow-up in a cohort of 41 primary progressive patients with multiple sclerosis (Ingle *et al* 2003). The rates of atrophy appeared relatively constant within individual patients but varied between subjects.

Atrophy, however, is not confined to advanced stages of the disease. Brain atrophy is also seen in established relapsing–remitting multiple sclerosis within 3 years of the onset of symptoms (Chard *et al* 2002a). Both white and grey matter atrophy are observed (Chard *et al* 2002a; de Stefano *et al* 2003). Even early follow-up of patients with clinically isolated syndromes has shown that significant brain atrophy emerges over 1–3 years in those subjects who later develop multiple sclerosis. This is most clearly seen in the grey matter and also as progressive ventricular enlargement (Dalton *et al* 2002b; 2004a). The apparent absence of progressive white matter tissue loss at this early stage of disease may reflect bulk tissue compensation by inflammation or gliosis (Fernando *et al* 2004). Possibly, grey matter atrophy will be a more sensitive measure of neuroaxonal loss because inflammation is less evident in this location (Bo *et al* 2003b; Petersen *et al* 2001). Atrophy of about 10–15% has also been observed in the optic nerve following a single attack of optic neuritis (Hickman *et al* 2001). We discuss later the evidence for atrophy as an outcome in the context of specific clinical trials.

From these data emerge a crucial lesson for the pathogenesis of multiple sclerosis and the timing of its treatment. The point is made repeatedly throughout this and other chapters. Despite effective suppression of inflammatory MRI lesions, treatments may not slow the rate of ongoing cerebral atrophy (Coles *et al*

1999a; Filippi *et al* 2000a; 2000b; Molyneux *et al* 2000) or have only a modest effect (Filippi *et al* 2004b). While differences in tissue loss from baseline can be detected in multiple sclerosis within 12 months, little work has been done to determine the optimal sample sizes and length of study required to demonstrate significant slowing of progressive atrophy as a result of therapeutic intervention. This is a priority area for further research, which should include consideration of the stage of disease, type of data acquisition, method of image analysis, region of the central nervous system being studied, frequency of scanning, and other potential confounding factors such as age or concomitant atrophy due to reduction of oedema.

Magnetic resonance spectroscopy: *N*-acetyl aspartate (NAA)

The main peak in the proton MR spectrum from human adult brain is *N*-acetyl aspartate (NAA), an amino acid contained almost exclusively in neurons and axons. A reduction in NAA provides evidence for axonal dysfunction or loss, and has been consistently reported in lesions and normal-appearing white matter in multiple sclerosis (Fu *et al* 1998). A greater reduction of normal-appearing white matter NAA is observed in secondary and primary progressive than relapsing–remitting multiple sclerosis, and disability has been correlated with reduced NAA in both cerebral (Sarchielli *et al* 1999) and cerebellar (Davie *et al* 1995) tissue. Decreased NAA (by 7%) has also been observed in cortical grey matter in early relapsing–remitting multiple sclerosis, suggesting that early neuronal cell body damage is occurring (Chard *et al* 2002b). It is reduced by c. 20% in thalamic grey matter in secondary progressive multiple sclerosis and, in a post-mortem study, the decrease in NAA (accompanied by atrophy) was associated with reduced numbers of neurons (Cifelli *et al* 2002).

Two approaches have been used to measure NAA: an absolute measure of concentration using an external standard reference of known concentration; and a ratio of NAA : Cr which assumes that Cr (creatine and phosphocreatine) remains stable in pathological situations. Although both approaches have produced robust evidence that NAA is reduced in the lesions and normal-appearing tissues, abnormalities of Cr may also occur. Therefore absolute measures are preferable. A methodological approach of recent interest is the quantification of whole brain NAA (Gonen *et al* 2000). This has been reported as low in patients with clinically isolated syndromes, implying extensive axonal damage even at this very early stage of disease (Filippi *et al* 2003). However, the resonance for whole brain NAA is broad and requires manual delineation for quantification – its analysis is potentially subject to bias and poor reproducibility. In contrast, the narrow NAA resonances from small voxels, obtained as a single region or as part of a spectroscopic imaging slice, can be automatically identified and quantified with a model that uses as reference a solution with a known concentration of NAA (Provencher 1993). Using such an approach, the normal-appearing white matter in patients with clinically isolated syndromes does not reveal a significant reduction of NAA (Fernando *et al* 2004). The time of onset and location of neuroaxonal damage should therefore be considered as uncertain.

A limitation of spectroscopy is the low signal to noise ratio and modest reproducibility of the measured metabolite concentrations. For this reason, it has been little used in multicentre therapeutic trials. Highlighting the problem, two small single-centre studies of patients treated with IFN-β have produced conflicting results. One study showed an increase in NAA, suggesting that therapy induced reversal of axonal dysfunction (Narayanan *et al* 2001). The other showed a decrease in NAA indicating that progressive axonal loss continues despite treatment (Parry *et al* 2003). Nevertheless, more vigorous efforts to investigate NAA as a surrogate outcome in trials of neuroprotection in multiple sclerosis are warranted, given that it provides specific information on axonal survival and function.

Diffusion tensor imaging

Diffusion tensor imaging offers potentially more specific access to the integrity of white matter tracts. Fractional anisotropy indicates the orientation of diffusion and is high along well-defined pathways such as the corpus callosum, pyramidal tracts and optic radiations. A reduction in such pathways is therefore a potential marker of axonal structural integrity. Algorithms have been developed for identifying individual white matter tracts. Diffusion tractography can be performed using several approaches (G.J. Parker *et al* 2002). Problems arise where pathways cross and there are sharp bends in the tract. However, tractography algorithms can quantify the size and fractional anisotropy of major pathways in the brain such as optic radiation and pyramidal tract (Ciccarelli *et al* 2000b; 2003a).

Other global measures

Many other quantitative MR measures have been applied to the study of multiple sclerosis. These include magnetization transfer ratio (MTR), T_1 relaxation time, and the apparent diffusion coefficient. Such measures are sensitive in depicting subtle abnormalities in normal-appearing white and grey matter, and convincing evidence has emerged that increasing abnormality in these tissues is associated with clinical progression (Filippi *et al* 1999a; Traboulsee *et al* 2003). However, these subtle MR changes do not denote specific pathological findings and could potentially represent the effects of inflammation, gliosis or axonal loss, each of which occurs in normal-appearing white matter (D.H. Miller *et al* 2003b). MTR may be valuable for monitoring clinically relevant disease progression in clinical trials. In a recent placebo-controlled study of IFN-β in secondary progressive disease, there was a significant increase in whole brain MTR abnormality in both the treated and placebo arms but no beneficial effect of treatment (Inglese *et al* 2003). This finding is consistent with lack of efficacy in the context of progressive disability. However, it is important to remember that progressive MTR abnormality may not be specific for neurodegeneration.

The process of neuronal and axonal degeneration is diffuse throughout the central nervous system and becomes more prominent with increasing disability and the progressive phase of multiple sclerosis. The two most specific MR methods for detecting neuroaxonal loss are atrophy and decreased NAA. For several reasons, atrophy has emerged as the preferred method for monitoring the neurodegenerative process in multiple sclerosis. Robust methods for detecting tissue loss are available. It is progressive from onset and increases with disability, correlates

only modestly with inflammatory lesions, and thus provides additional information in therapeutic monitoring. Whereas a number of existing therapies have shown good suppression of inflammatory lesions, an effect on progressive atrophy has been less evident (for review, see D.H. Miller *et al* 2002). Although other MR markers of diffuse disease (such as MTR) are not specific for axonal loss, along with atrophy they provide sensitive measures of a diffuse, progressive underlying process that relates to clinical progression. MTR measurement in lesions may have a more specific role in therapeutic monitoring in that decreases and increases (which are larger than the subtle changes seen in normal-appearing tissues) may reflect demyelination and remyelination, respectively (Barkhof *et al* 2003; Schirmer *et al* 2004).

It is therefore recommended that atrophy should be measured in trials aiming to prevent disability at all stages of disease (clinically isolated syndromes, relapsing–remitting, primary and secondary progressive) and, where feasible, NAA should also be measured along with other techniques (such as MTR) to monitor progressive normal-appearing white and grey matter. It is nevertheless important to remember that the MR surrogates for neuroaxonal loss and diffuse disease have not yet unambiguously been shown to predict future disability and its prevention by treatment. Long-term follow-up studies of well-characterized cohorts, including those participating in controlled clinical trials, are needed to clarify this relationship. Meanwhile, definitive trials should continue to measure an appropriate clinical end point.

DRUGS THAT STIMULATE THE IMMUNE RESPONSE

In the past, attention was more or less equally divided between strategies designed to stimulate the immune system (initially, in the belief that immunological injury is sustained by persistent viral infection) or provide specific antiviral therapy, and those that suppress immunity. Now, it is clear that immune stimulants are either not effective or increase disease activity – perhaps as a result of increased expression of class II major histocompatibility complex (MHC) antigens on antigen-presenting cells. Some of these discarded treatments are briefly reviewed as part of the evidence that suppression of immunity and inflammation, not its stimulation, holds most promise for modifying the clinical course of multiple sclerosis.

Isoprinosine

Isoprinosine is a physicochemical complex of inosine and the para-acetamidobenzoic acid salt of *N*,*N*-dimethylamino-2-propranolol, that enhances B-lymphocyte activity, perhaps through an effect on T helper cells. It also increases macrophage phagocytosis, release of cytokines that induce macrophage proliferation, including immune interferon and interleukin-1 (IL-1) and IL-2, and augments the action of T-cell mitogens (Hadden and Speafico 1985). Pompidou *et al* (1986) compared the clinical and immunological effects of isoprinosine, chlorambucil and a placebo preparation in a small cohort of patients with multiple sclerosis over 2 years. Relapses occurred in all patients treated with chlorambucil or placebo but in only a minority of those receiving isoprinosine. Relapses did not differ in severity between the three groups but the authors reported a reduction in disability associated with the use of isoprinosine. Immunological studies showed increased suppressor cell number and function in isoprinosine-treated cases, whereas cells with the T helper phenotype and delayed-type hypersensitivity were reduced in patients receiving chlorambucil.

Milligan and Compston (1994) used isoprinosine under double-blind, randomized and placebo-controlled conditions in 52 patients with relapsing–remitting or progressive multiple sclerosis. All patients initially received pulsed treatment with methylprednisolone. There was no significant effect of treatment on clinical disability or the accumulation of MRI abnormalities, after correction of results for multiple comparisons.

Linomide

Linomide is an immunomodulator that appears primarily to affect natural killer cells without inducing the release of IFN-γ. It also increases T-cell proliferative responses, the proportion of the CD45-Ra-positive subpopulation and IL-2 production. Its use in multiple sclerosis arose from the apparent ability of linomide to prevent and reverse the clinical and histological manifestations of experimental autoimmune encephalomyelitis (see Chapter 11). Karussis *et al* (1996) evaluated linomide (2.5 mg/day for 6–12 months) in 24 patients with secondary progressive multiple sclerosis who had deteriorated by >1 EDSS point in the previous 2 years, and showed either three regular or one enhancing MRI lesions on a single screening scan. There were no major adverse effects although minor events were reported in a high proportion of all participants. On this evidence, linomide appeared safe. An increase in disability (EDSS) at 6 months occurred in three of the 15 linomide-treated patients, and in six of the 15 placebo-treated patients; five and two of the 15 cases improved, respectively. Active lesions were present in 16% of linomide-treated patients and 33% of the placebo group at onset. Subsequently, 11 of 33 (33%) and 24 of 32 (75%) had active scans, with a difference in mean number of new enhancing lesions of 0.2 and 0.4 per scan, respectively.

Andersen *et al* (1996) reported a somewhat greater range and prevalence of adverse effects (one requiring drug withdrawal and another a reduction in dose) in 28 patients with relapsing multiple sclerosis randomized to oral linomide (2.5 mg/day for 6 months). MRI showed a lower rate of active T_2-weighted lesions in treated patients (1.4 compared with 4.2 in the placebo group; 0.8 and 2.6 for new lesions, respectively; constituting a 68% reduction in activity) and this effect seemed to increase with the duration of treatment. Three patients on linomide had four relapses and six of the placebo group had nine new episodes. Whilst the placebo group showed no change in disability, patients on linomide had a modest reduction in EDSS (–0.4). The numbers who improved, remained unchanged or deteriorated were ten, one and three in the treated group, respectively, compared with five, one and eight in the placebo-treated patients.

Enthusiasm for the use of linomide in multiple sclerosis collapsed with the decision to terminate early the North American and European phase III trials after enrolling >1380 patients with relapsing–remitting and secondary progressive multiple sclerosis because of serious cardiopulmonary and other adverse effects in the treated groups (Noseworthy *et al* 2000c; I.L. Tan

et al 2000; Wolinsky *et al* 2000). Two linomide-treated patients died in the course of the trial from suspected cardio-pulmonary complications of linomide, but autopsies were not performed. An unacceptable number of patients treated with linomide developed pleuro-pericarditis (nine patients), chest pain, myocardial infarction (five patients), and possible pulmonary embolic disease as well as arthralgia, myalgia, bursitis and facial and peripheral oedema. These trials again emphasize that experimental treatments can place patients at risk of life-threatening adverse events. The importance of scrupulous surveillance by data-monitoring committees cannot be overstated. If there are safety concerns, immediate action may be needed to lessen risks to patients. Unless a preventable mechanism for these events becomes apparent, it looks as if linomide will join the ranks of drugs no longer to be used in patients with multiple sclerosis. However, Polman *et al* (2005) have recently studied the oral agent laquinimod (ABR-215062), a synthetic compound structurally related to roquinimex (linomide) in a randomized, double-blind, placebo-controlled trial of 209 patients with multiple sclerosis in three groups (laquinimod 0.1 mg or 0.3 mg, or placebo daily for 6 months). There were no serious adverse side effects (notably, no cardiopulmonary events or serositis; see above for linomide). High-dose laquinimod reduced the frequency of active MRI lesions significantly compared with placebo. These results, if confirmed in a larger controlled trial of sufficient duration and statistical power, suggest reasons for optimism in the search for oral agents that might one day simplify the management of relapsing–remitting multiple sclerosis.

Interferon-γ

The clinical trial of IFN-γ reported by Panitch *et al* (1987a, 1987b) proved extremely influential because it made patients worse and so told an important story (Figure 18.2). The logic for using IFN-γ was based on the hypothesis that multiple sclerosis is caused by persistent viral infection or an immunoregulatory defect that requires stimulation. If the study had shown clinical benefit in such a small group of patients, replication would have been immediately demanded, but this result was readily accepted because, at the time of publication, knowledge of autoimmune processes had advanced to the stage where it could be predicted that disease activity would increase with promotion of class II MHC molecule expression. Panitch *et al* (1987a; 1987b) recruited 18 patients known retrospectively from case records to have had two or more relapses in the previous 2 years. All were in remission and ambulatory at the start of treatment. Follow-up was to be for 6–12 months after receiving three doses of IFN-γ (1, 30 and 1000 mg by intravenous injection) on eight occasions over 4 weeks. Within 1 month of treatment, seven of the patients had experienced a new relapse. Based on pretreatment rates, no more than two relapses were expected. Onset and severity were unrelated to the dose given. Recovery was complete and the relapse rate stabilized during follow-up at the former frequency with no overall change in disability. There was an increase in MHC class II-positive circulating lymphocytes. The implication of the study was that systemic IFN-γ had a rapid and causal effect on stimulating inflammatory processes within the central nervous system. In their discussion, the authors recommended others to assess treatments, including IFN-α and IFN-β, that specifically inhibit IFN-γ. Not surprisingly, this study is often cited as a clear example of clinical science in which lessons learned from the experience of treatment led to new concepts of disease mechanisms and, in turn, the development of more rational and effective therapies. Self-evidently, there are no subsequent studies on which to comment.

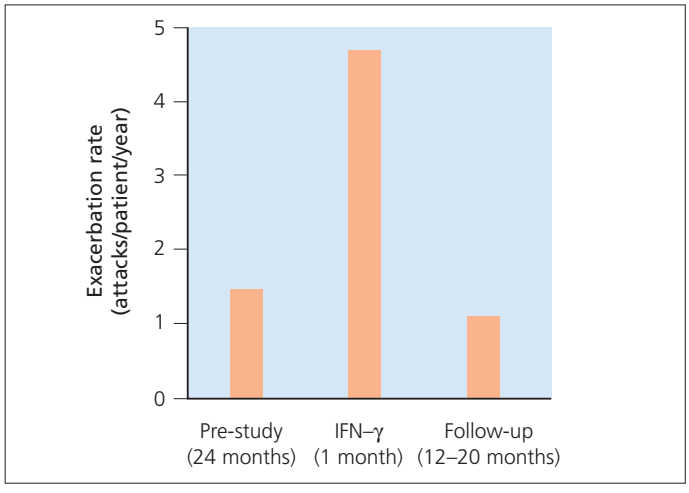


Figure 18.2 Increase in exacerbation rate during treatment with IFN-γ compared with pretreatment and follow-up periods. Adapted from Panitch *et al* (1987b). © 1987, with permission from Elsevier.

Interferon-α

The demonstration of a deficient interferon response in patients with multiple sclerosis stimulated the use of IFN-α at a time when the adverse effects of IFN-γ and the logic for using anti-inflammatory cytokines were not fully understood. Fog (1980) failed to show a beneficial effect on the disease course over 18 months in six patients with chronic progressive multiple sclerosis openly treated with intramuscular IFN-α. Next, Knobler *et al* (1984) reported fewer and shorter new episodes during IFN-α treatment in 24 patients with relapsing multiple sclerosis compared with retrospective assessment of relapse frequency over 2 years before starting the trial. Although the crossover design made for difficulties in judging the magnitude of this treatment effect, there was a reduction in relapse frequency with time in all participants. This was most apparent in patients receiving IFN-α after the placebo period. The reduction in relapse rate was maintained and improved in those patients showing a treatment effect over the initial 2 year period of observation in the subsequent 2 years, but the extent to which this could be attributed to treatment rather than to the natural history of the disease remained uncertain. Compared with the relapsing–remitting patients, those with relapsing progressive disease demonstrated evidence of mild to moderate symptom worsening during the prestudy period and they continued to have exacerbations during treatment (Figure 18.3). There was no effect on disability (Panitch 1987). Recombinant IFN-α, given by self-administered subcutaneous injection three times weekly for 1 year, was first used in a study of 98 patients with multiple sclerosis with at least two relapses during the previous 2 years. The results were not encouraging. All patients showed a reduction in relapse rate as part of the natural history of the

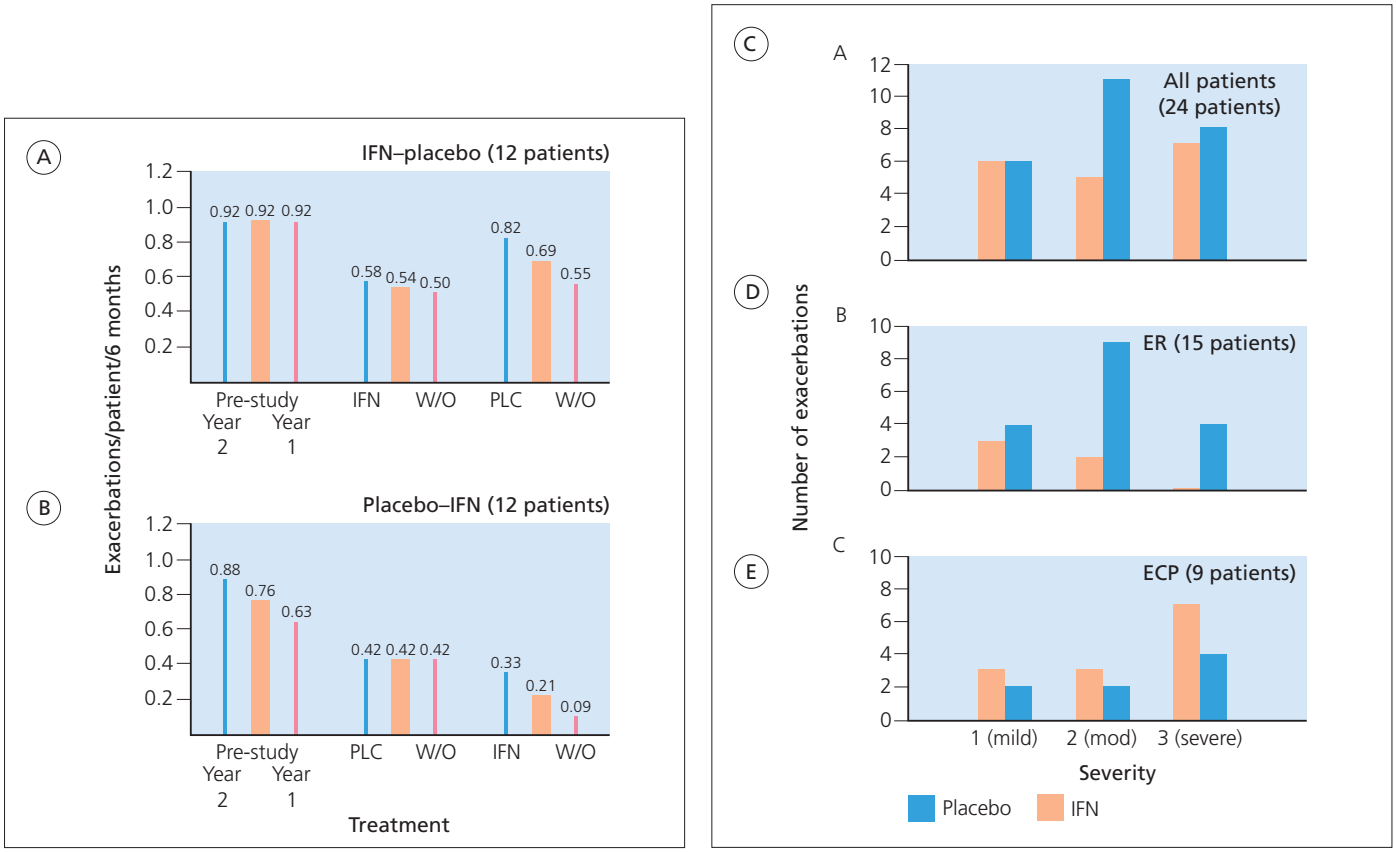


Figure 18.3 Treatment of multiple sclerosis with IFN-α. (A and B) Relationship between treatment sequence and response. The effect of interferon (IFN), placebo (PLC) and respective washout (W/O) periods on mean number of exacerbations/patient/6 month period are indicated by red and blue solid lines. The orange bars are average values for the flanking red and blue lines. Exacerbations occurring during prestudy year 2 or year 1 are also expressed per 6 month period. There is a greater reduction in exacerbation frequency associated with the PLC–IFN sequence than the IFN–PLC, which may reflect carryover effects of the crossover design or composition of the two groups. (C–E) Relationship between subgroup of multiple sclerosis patients, treatment and exacerbation severity. The latter was graded as mild (MLD), moderate (MOD) or severe, dependent on change in the Scripps (SNRS) score and duration of the exacerbation in days, during IFN and placebo treatment and respective washout periods. (C) IFN did not appreciably alter exacerbation severity when all 24 patients were compared. (D) However, the 15 exacerbating–remitting (ER) patients had no severe and fewer moderate exacerbations ($p = 0.10$) on IFN compared with placebo. (E) In contrast, the nine exacerbating chronic progressive (ECP) patients had more exacerbations of each grade during IFN treatment than during placebo treatment. Adapted from Knobler *et al* (1984). © 1984, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

disease. However, more treated than placebo cases moved from the relapsing to the progressive phase of the disease and, unlike those on placebo preparations, treated cases experienced an increase in disability after discontinuing treatment (Camenga *et al* 1986).

It is perhaps surprising that, in the face of these results, Durelli *et al* (1994) repeated the study of IFN-α given by intramuscular injection on alternate days to patients with relapsing–remitting multiple sclerosis. Individuals on IFN-α showed a lower exacerbation rate (Figure 18.4), longer time to first relapse, and milder episodes less often requiring supplementary treatment with corticosteroids compared to the placebo group. However, disability was unaffected. Fatigue and other systemic adverse effects associated with the use of interferon were the main complications of treatment. There was an effect on disease activity measured by MRI. One of 12 patients on active treatment had a single enlarging lesion (which corresponded to a new clinical episode) whereas six of the eight controls had both new and enlarging lesions (27 of either type, equivalent to five for each active scan). The treated group also showed some suppression in the systemic production of IFN-γ.

In a follow-up study, Durelli *et al* (1996) examined the resumption of clinical, MRI and immunological activity in patients who had to discontinue IFN-α (after 6 months of treatment) for administrative and financial reasons. In the four 6 month epochs preceding treatment, the numbers of patients remaining relapse free in the 12 patient cohort later randomized to IFN-α were two, one, four and three. The numbers without episodes in the group of eight patients randomized to placebo were two, zero, three and one, respectively. Against the background of these baseline estimates, two further relapses occurred during treatment with IFN-α compared with eight in the placebo group. In the 6 months after completion of the active treatment phase, there were three relapses in individuals who had received IFN-α compared with four in the placebo group. The numbers of patients remaining relapse free during and after the period of treatment with IFN-α were ten and nine, compared with two and four of the eight patients in the placebo

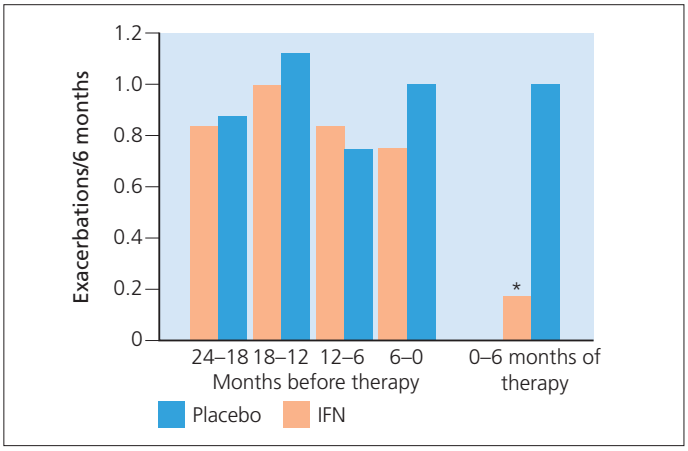


Figure 18.4 Exacerbation rate (calculated on a 6 month basis) in the 2 years before and during treatment for patients receiving high-dose systemic recombinant IFN-α2a (IFNA) or placebo. Asterisk indicates significantly different from prestudy ($p \leq 0.03$) and from placebo ($p \leq 0.03$) groups. Adapted from Durelli *et al* (1994).

group. Taken together, these observations suggest a transient increase in the number of relapse-free patients during treatment with IFN-α.

The MRI results also suggested a transient reduction in disease activity which reversed on discontinuing treatment with IFN-α. There was one active lesion in the IFN-α patients during treatment and 14 after treatment, compared with 27 and 17 in the placebo group, repectively. Corresponding results for the number of active scans were one (during) and six (after) of the 12 IFN-α-treated patients, compared with six and six for the placebo group. There was no obvious effect on disability during treatment or apparent acceleration after discontinuing IFN-α. Durelli *et al* (1996) concluded that two of the 12 patients receiving IFN-α and seven of the eight placebo-treated patients had active disease during treatment, compared with six (IFN-α-treated) and six (placebo-treated) after completion of the active treatment phase. Immunological assessments showed that reduced IFN-γ and TNF-α levels, associated with the use of IFN-α for 6 months, also returned to baseline values on discontinuing treatment. Adverse effects attributed to the use of IFN-α were reversed within 1 or 2 months of treatment. This study adds to the evidence that clinical, radiological and immunological observations can directly be attributed to IFN-α, but are rapidly washed out on discontinuing treatment.

Myhr *et al* (1999b) randomized 97 patients with relapsing–remitting multiple sclerosis to receive either 4.5 or 9 million international units (MIU) of IFN-α2a or placebo, by subcutaneous injection three times weekly for 6 months. Relapses were not reduced although monthly MRI measures suggested a possible benefit during the period of treatment. The authors reported that neutralizing antibodies developed early in the group given low-dose IFN-α, and they speculated that this may have reduced the treatment effect. However, as discussed below, in most of the large-scale recent IFN-β trials, changes in clinical and MRI measures of disease activity correlating with antibody formation are generally difficult to detect unless a large number of patients are followed up for a protracted period. Brod *et al* (2001) reported that oral IFN-α2a (10 000 or 30 000 units administered on alternate days for 9 months) was no better than placebo in suppressing MRI evidence of disease activity in a study of 30 patients with relapsing–remitting multiple sclerosis. However, despite some favourable results, we understand that IFN-α is not to be developed further for use in patients with multiple sclerosis.

Transfer factor

Although the biological properties of IFN-α were already characterized, patients with multiple sclerosis were also treated in the 1980s with transfer factor – a dialysable leucocyte extract thought to restore cell-mediated immunity and to have antiviral actions similar to IFN-α and IFN-β. The AUSTIMS Research Group (1989) compared these two biological reagents [IFN-α (3×10^6 units); transfer factor (0.5 units) made from the leucocytes of cohabitees to maximize the prospect of achieving specificity against whatever agent might be causing multiple sclerosis] with placebo preparation(s) in 182 patients. There was no stratification for relapsing versus progressive disease. Clinical outcome was assessed using the EDSS. There was no difference in progression of disability between groups and no apparent effect of treatment on laboratory indices. In fact, the only clear result was that transfer factor was poorly tolerated and many individuals withdrew from the treated group. Soon after, van Haver *et al* (1986) treated 105 patients with multiple sclerosis (a mixed group with relapsing–remitting and secondary progressive disease) using transfer factor prepared from the leucocytes of random donors or family members. They also failed to demonstrate an effect on disability, activities of daily living or laboratory indices of demyelination. Treatment did not affect IFN-γ production.

Aciclovir

Although not strictly an immune modulator, we include discussion of the antiviral treatment, aciclovir, because (as with IFN-γ) it has been used on the basis that tissue injury in multiple sclerosis might result from persistent viral infection. Aciclovir (2.4 g orally for 2 years) has been evaluated in 60 patients with frequent relapses but very few persistent disabilities (C. Lycke *et al* 1996). There was a reduction in relapse frequency (from 1.7 to 1.0 in the aciclovir group and from 1.7 to 1.6 in placebo-treated patients; $p = 0.08$). Aciclovir did not affect the time to first and second exacerbations over the 2 years of the study. Despite the reduction in relapse rate, patients accumulated clinical deficits at an equivalent rate in both groups and there was no difference in disability on completion of the study. This dose of aciclovir achieved some reduction in herpes simplex virus-2 but not varicella zoster, Epstein–Barr virus or cytomegalovirus antibody titres. As expected, aciclovir was well tolerated with few adverse effects.

A second phase two, randomized, double-blinded, placebo-controlled study of anti-herpes therapy was reported by Bech *et al* (2002). They compared valaciclovir (1 g orally three times daily for 24 weeks) with placebo in 70 patients with relapsing–remitting multiple sclerosis. To be eligible, patients needed to have a history of two or more relapses in the previous 2 years yet still be ambulatory (EDSS 0–5.5). The primary outcome

(number of new active MRI lesions over the 24 week course of the trial) was negative (valaciclovir: 11.9 ± 17.6 SD; placebo 14.5 ± 21.4 SD) and there were no differences in any of the clinical end points. A planned exploratory analysis detected that the valacilovir-treated patients who had at least one active MRI lesion during the pretreatment phase of the trial (4 weeks plus baseline MRI) had fewer new MRI lesions and were more likely to remain free of new MRI evidence for disease activity during the treatment period. An accompanying editorial encouraged further well-designed trials with antiviral agents while acknowledging that valaciclovir at conventional doses has no apparent role in the treatment of multiple sclerosis (Goodman and Miller 2002). Friedman *et al* (2005) reported that a placebo-controlled, randomized trial of valaciclovir (3000 mg/d) involving 58 patients with multiple sclerosis failed to demonstrate convincing clinical or MRI evidence for benefit although there were statistical trends in favour of some outcomes in the most severely affected patients.

Against this background, the further use of drugs that are known to stimulate one aspect or another of the immune response seems inappropriate and unlikely to satisfy scrutiny by ethical committees. Rather, the focus of therapeutic attention has turned to a range of strategies that have in common suppression of the immune response. It would take a very churlish observer to conclude that nothing has been learned and no patients helped from this approach (but such therapeutic nihilists exist). Equally, no informed critic could reasonably argue that the achievements to date are anything other than modest and represent no more than an indicator of the way forward. Perhaps, the crucial limitation has been the timing of treatment and the exposure of patients to drugs that are not fully appropriate for the stage reached in the illness by that particular patient. Now, we review in detail the various drugs that suppress one aspect or another of the immune response through a variety of mechanisms – some identified, others mysterious.

DRUGS THAT NONSPECIFICALLY SUPPRESS THE IMMUNE RESPONSE

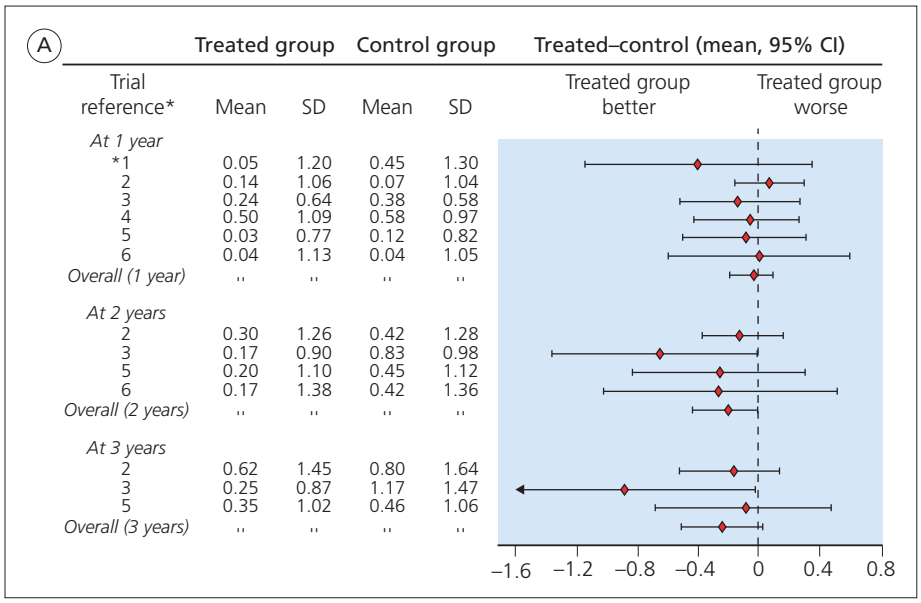
Advances in understanding the nature of tissue injury in multiple sclerosis, and the lessons from attempts to stimulate the immune response and so purge the nervous system of persistent viral infection, prompted the use of drugs that suppress the immune response. This seemed logical even though most inflict prolonged punishment on the whole immune system for the misdemeanours of a small proportion of its constituent cells.

Azathioprine

Azathioprine, used for many years to treat individual patients with multiple sclerosis, was evaluated in clinical trials during the 1970s and 1980s (Mertin *et al* 1982; U. Patzold *et al* 1982; Rosen 1979; Swinburn and Liversedge 1973). The possibility that this reasonably well-tolerated nitroimidazole substituted form of 6-mercaptopurine might reduce progression of the disease in patients with moderately severe forms of multiple sclerosis prompted the (United Kingdom) Medical Research Council to sponsor a double-blind, placebo-controlled trial involving 354 unselected patients, on the advice of its working party on clinical trials (British and Dutch Multiple Sclerosis Azathioprine Trial Group 1988b). There was slower deterioration and fewer relapses in patients treated with azathioprine but these differences were not statistically significant or considered clinically useful for the individual patient. Other work in progress at that time was subsequently reported including a trial in which small numbers of patients were treated with azathioprine, methylprednisolone or placebo preparations. The treatment groups each contained fewer than 30 patients (Ellison *et al* 1989). No significant differences emerged, although subgroup analysis showed that patients tolerating the combination of active treatments deteriorated less rapidly. The authors recommended that, because of the poor risk to benefit ratio, azathioprine should not be given alone or with corticosteroids to patients with progressive multiple sclerosis. After publishing a preliminary account, and including their data in the meta-analysis of azathioprine (see below), Milanese *et al* (1993) subsequently provided a final report on their study of 40 patients with relapsing or chronic progressive multiple sclerosis receiving 2 mg/kg/day for 3 years. There was a very high drop-out rate but the authors concluded, on an intention to treat analysis, that a treatment effect was demonstrated on relapse rate (90% remained relapse free on azathioprine vs. 60% of the placebo group) and the proportion of patients remaining clinically stable (62% vs. 18%).

Kappos *et al* (1990) reported on 37 matched pairs selected retrospectively from amongst 277 with clinically definite multiple sclerosis who had all been fully ambulant when treatment with azathioprine was started >10 years previously. Six treated patients were bedridden and four had died compared with 13 and eight, respectively, amongst untreated historical controls. The mean EDSS at 10 years was less in the azathioprine-treated group (4.9 vs. 6.0). There were similar numbers of patients in both groups who remained nearly normal (EDSS 0–2.5), reflecting again the important observation that a subgroup of untreated patients with multiple sclerosis remain with limited disability for prolonged periods. Goodkin *et al* (1991) also showed a lower relapse rate in 43 of 59 patients recruited to a study of azathioprine (3 mg/kg/day) compared with placebo in relapsing multiple sclerosis. Annual pretreatment, year 1 and year 2 rates in the azathioprine and control groups were 1.6, 0.7 and 0.3 and 1.5, 1.2 and 0.8, respectively. The numbers having a relapse in years one and two, for each group, were 16 and 7, and 17 and 11, respectively. The proportions showing progression in the EDSS and ambulation index in the treated group were 19% and 22% compared with 32% and 40%, respectively, in the placebo group. Not surprisingly, azathioprine does not prevent the onset of multiple sclerosis. Constantinescu *et al* (2000) described two patients developing multiple sclerosis after treatment for inflammatory bowel disease with azathioprine after 3.5 and 10 years, respectively.

Against this background of small studies suggestive of a treatment effect, Yudkin *et al* (1991) performed a meta-analysis of published trials. Ten were considered, of which seven were included. In five, the design was double-blind and placebo-controlled but not all had been analysed on an intention to treat basis. Of the 793 participants, 719 (91%) were followed for at least 1 year, 563 for 2 years and 459 for 3 years (with information available on 94% and 90%, respectively). Patients with relapsing–remitting and both primary and secondary progressive multiple sclerosis were included but evenly distributed between



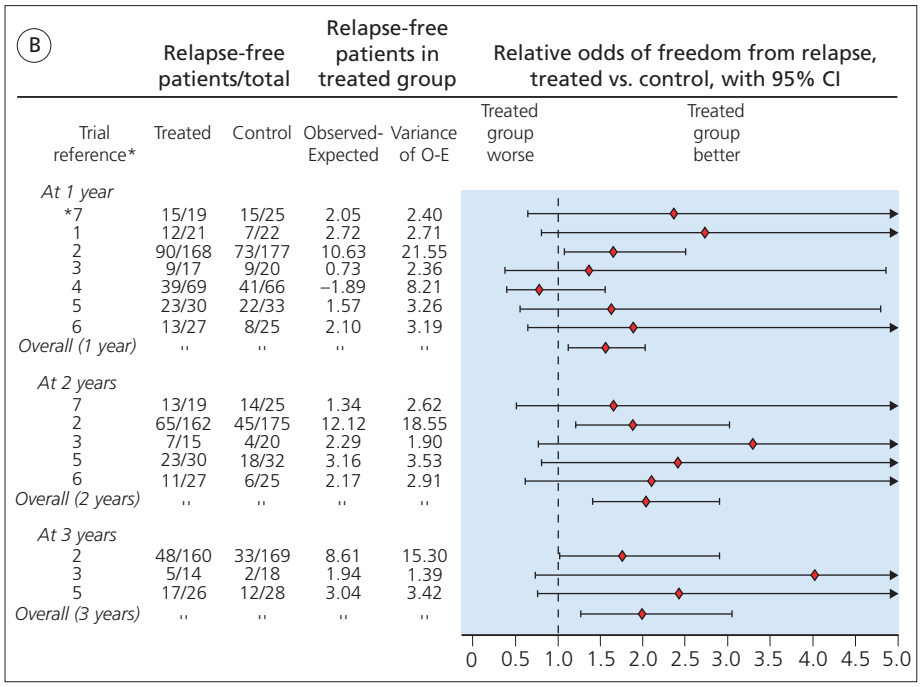


Figure 18.5 Meta-analysis of treatment trials using azathioprine in multiple sclerosis. (A) Changes in [E]DSS. (B) Probability of freedom from relapse. Adapted from Yudkin *et al* (1991). References: 1 = Mertin *et al* (1982); 2 = British and Dutch Multiple Sclerosis Azathioprine Trial Group (1988); 3 = Milanese *et al* (1988); 4 = Ghezzi et al (1989); 5 = Ellison *et al* (1989); 6 = Goodkin *et al* (1991); 7 = Swinburn and Liversedge (1973). © 1991, with permission from Elsevier.

active and placebo treatment groups. The odds ratio for a treatment effect achieving a reduction in the EDSS attributable to azathioprine was –0.03 (95% CI –0.19, +0.12) but this had increased after 2 and 3 years to –0.22 (95% CI –0.43, +0.003; $p \leq 0.06$) and –0.24 (95% CI –0.51, +0.03; $p < 0.09$: Figure 18.5A). The probability of remaining free from relapse, attributable to azathioprine, at 1, 2 and 3 years was 1.5 (95% CI 1.1–2.0; $p < 0.01$), 2.0 (95% CI 1.4–2.9; $p < 0.001$) and 2.0 (95% CI 1.3–3.0; $p < 0.01$), respectively (Figure 18.5B).

Although the mode of action of azathioprine is well established, little is known concerning its effects on those aspects of immunity considered most relevant to multiple sclerosis. Salmaggi *et al* (1997) compared a range of immunological markers in individuals receiving up to 3 mg/kg azathioprine daily and untreated patients with multiple sclerosis. Therapy was characterized by pan-neutropenia which disguised selective increases attributable to azathioprine in the proportion of lymphocytes coexpressing the CD3/4, CD3/56, CD3/16 and CD4/45Ra markers, with a corresponding reduction in natural killer cells (but not natural killer cell activity) and TNF-α production. There was no effect on immunoglobulin production despite the increase in CD4/45Ra cells. These findings do not obviously enhance our understanding of the immunopathogenesis of multiple sclerosis or provide an independent logic for reintroducing azathioprine as a disease-modifying treatment in multiple sclerosis.

Reduction in relapse rate with a delayed and modest effect on disability anticipates results subsequently obtained using the currently licensed therapies but the tone of discussion around these earlier treatments could not have been more different. The meta-analysis of azathioprine is a model of caution and

understatement, emphasizing that the effects are modest, probably explained by interobserver variation, of doubtful value to the individual patient, quite possibly attributable to unblinding, and potentially posing serious long-term risks. Nevertheless, until the advent of IFN-β, many clinicians used azathioprine in patients with multiple sclerosis despite general concern over the long-term risks (Kinlen 1985). Reassuringly, Amato *et al* (1993) provided evidence against an increased rate of malignancy in patients with multiple sclerosis receiving azathioprine. Five of 207 patients taking 2 mg/kg daily for a mean of 4.2 years developed a malignancy compared with seven of 247 controls, giving prevalence rates of $3.6/10^3$ patients (95% CI 1.2–8.4) and $4.2/10^3$ patients (95% CI 1.7–8.7) and a relative risk (RR) of 0.8 (age adjusted) for cancer in the treated patients with multiple sclerosis. In a more detailed assessment, Confavreux *et al* (1996) showed in a case–control study that 14 of 23 patients with multiple sclerosis who developed one form or another of cancer had been treated with azathioprine for at least 1 month (RR = 1.7; 95% CI 0.6–4.6). There was a direct relationship between risk and duration of exposure (<5 years, RR = 1.3, 95% CI 0.4–4.0; 5–10 years, RR = 2.0, 95% CI 0.4–9.1; >10 years: RR = 4.4; 95% CI 0.9–20.9). Nevertheless, adverse effects appear to influence decisions over the use of azathioprine.

Most clinicians concluded, when these studies were published, that the clinical benefits of azathioprine fall short of satisfactory treatment for the individual patient, and as new immunosuppressants became available, they were evaluated in the hope that the new medicines would prove more effective. Nevertheless, azathioprine has not disappeared from the list of drugs used in multiple sclerosis. Some consider that prolonged oral azathioprine is no less effective than IFN-β and glatiramer acetate – since efficacy was not evaluated using MRI outcomes at the time opinions were being formed. Later, Massacesi *et al* (2000) reported that MRI measures of disease activity were reduced by treatment with azathioprine in 14 patients followed for 2 years. Meanwhile, Palace and Rothwell (1997) reviewed published data for the 2 year probabilities of freedom from relapse with each of the approved but partially effective agents including azathioprine and compared these projections with the observed outcomes of placebo-treated patients from these studies. The overall odds ratios for an effect on relapse rate demonstrated that oral azathioprine may indeed be comparable to the now more widely used parenteral agents (glatiramer acetate, 1.37; IFN-β1a, 1.68; IFN-β1b, 2.38; intravenous immunoglobulin, 2.01; and azathioprine 2.04) – and at a fraction of the cost (Clegg and Bryant 2001).

The recent trend has been to use azathioprine in combination with other therapies. Intravenous immunoglobulin was given in divided doses (total 2 g/kg) over 72 hours followed by monthly infusions of 0.2 g/kg for 3 years to 38 patients with relapsing–remitting multiple sclerosis who also received oral azathioprine (3 mg/kg/day: Kalanie and Tabatabai 1998). Combination therapy was well tolerated by the 34 patients completing this trial. After 3 years of monthly evaluations by an assessor blinded to details of the protocol, no patients developed clinical evidence of worsening (relapse rate or disease progression). These results are rather remarkable, and more favourable than expected from experience with natural history and clinical trial data sets. However, the study was uncontrolled and, to date, has not been replicated. Moreau *et al* (2001) reported that the combination of azathioprine and IFN-β1a appears safe and well tolerated, at least for the 6 months of follow-up available at the time of abstract submission – but, to date, the study has not generated a full research publication. Recently, Lus *et al* (2004) reported their small prospective study of 23 patients treated with a combination of azathioprine and IFN-β1a (Rebif) followed for 2 years. For the purpose of data analysis, patients were considered in three groups: previously untreated individuals (n = 8) and patients previously treated with either azathioprine (n = 8), or IFN-β1a (n = 7). Combination therapy was safe and generally well tolerated. Relapse rates and MRI evidence of disease activity (T_2 lesions, contrast enhancements and T_1 hypodense lesions) were reduced in the prospective phase of the study compared with historical data. In a small study (n = 6), Markovic-Plese *et al* (2002) reported that the combination of azathioprine and IFN-β1b (Betaseron) provided synergistic effects on stabilization of the blood–brain barrier as determined by MRI studies.

Whilst alert to the changing landscape of treatment trends in multiple sclerosis, at present we do not routinely use azathioprine, pending evidence of superior efficacy and adequate safety from contemporary controlled trials but it remains an acceptable approach in patients who are unable to contemplate injected therapies. That said, Craner and Zajicek (2001) consider that, unlike those with myasthenia gravis or rheumatoid arthritis, the majority of patients with multiple sclerosis (55%) are unable to tolerate azathioprine. It has been recommended that levels of thiopurine methyltransferase should be measured in advance of a prescription, so as to avoid serious bone marrow toxicities (F.J. Thomas *et al* 2001; Weinshilboum and Sladek 1980).

Ciclosporin

Although not now routinely used in clinical practice or featuring in new trial protocols, we retain our earlier account of ciclosporin (formerly cyclosporine) for the lessons it provides in the evolution of ideas concerning the basis for treatment in multiple sclerosis. In a modest way, ciclosporin influences progression of multiple sclerosis, relapse rate and severity but only at doses that produce unacceptable adverse effects. Rudge *et al* (1989) showed no difference in the number of patients remaining relapse free between ciclosporin-treated and placebo-treated groups during a 2 year clinical trial. However, episodes were more frequent in the placebo group, and these were judged to be more severe and to have occurred earlier. More ciclosporin-treated patients than controls remained stable, in terms of the EDSS, over the first 6 months of the trial but this effect was not maintained thereafter. One difficulty that arose was the need to stratify the analysis to account for a centre effect. Selection of patients on the basis of clinical course and the dose of ciclosporin that was tolerated differed between the two participating centres. Critics therefore assume that, for many participants, the study was unblinded. They worry about the dependence on subgroup analysis and conclude that there is no clinical role for ciclosporin. We know of very few patients with multiple sclerosis in whom this immunosuppressant is still used. This trial taught the useful lesson that the course of multiple sclerosis is more likely to be altered by immunological treatments used at doses producing significant adverse effects that outweigh the modest clinical advantages. In a comparison with

azathioprine, low-dose ciclosporin is shown to be less well tolerated and no more beneficial in terms of disease stabilization (Kappos *et al* 1988). Although the participants experienced very little deterioration during the trial, this study was not designed to show that either drug influenced the natural history of the disease.

Subsequently, in a placebo-controlled study of ciclosporin involving 547 patients with moderate to severe progressive multiple sclerosis (EDSS between 3 and 7 with a change in the year before entry of between 1 and 3 points) treated with a range of doses, some aspects of disability were significantly influenced. However, a substantial number of patients withdrew from the active treatment group because of adverse effects, notably nephrotoxicity and hypertension (Multiple Sclerosis Study Group 1990). Reduction in the mean increase in EDSS in treated patients compared with controls (0.39 ± 1.07 vs. 0.65 ± 1.08; mean ± SD) was associated with delay in time to use of a wheelchair but not to sustained progression, and there was no effect on activities of daily living. Ruutianen *et al* (1991) compared ciclosporin (7.5 mg/kg) with oral prednisolone (tapering from 0.8 mg/kg). Despite no immediate difference in outcome, greater improvement was reported in patients on corticosteroids at 3 months. There was no difference in the frequency of adverse effects.

Taken together, clinicians are not persuaded that ciclosporin represents a significant advance over the modest effects associated with the use of azathioprine. Long-term oral therapy with azathioprine appears better tolerated but not sufficiently useful (see above), whereas ciclosporin is considered more effective but unacceptably complicated in patients with multiple sclerosis.

Cyclophosphamide

The same problems have characterized the evaluation of treatment with cyclophosphamide. This immunosuppressant has been used on an open uncontrolled basis for many years, especially in continental Europe. Attention was drawn to its use with the publication of a study reporting that high-dose intravenous cylcophosphamide stabilizes the clinical course in patients with progressive multiple sclerosis when given with corticotropin by comparison with patients receiving corticotropin alone, or plasma exchange with corticotropin and low-dose oral cyclophosphamide (S.L. Hauser *et al* 1983). By present standards, this study was of short duration and underpowered, only involving between 18 and 20 patients in each arm. Summarizing the quantitative observations in an overall qualitative assessment, four of the 20 patients receiving corticotropin stabilized or improved at 1 year, compared with 16 of the 20 patients in the cyclophosphamide/corticotropin group and nine of 18 patients in the plasma exchange. As a result of this trial, many patients received high-dose intravenous cyclophosphamide for several years, tolerating a variety of unpleasant short-term adverse effects in the hope of disease stabilization. Subsequent experience with dose ranging studies in which maintenance therapy was adjusted against indices of immune suppression (circulating CD4 counts) merely confirmed the potential toxicity of cyclophosphamide and led some to conclude that the drug is too toxic for routine use (L.W. Myers *et al* 1987). Nevertheless, an approach using repeated pulses of well-tolerated doses, given at monthly or longer intervals, was later evaluated in 14 patients using a partial crossover design. Those treated with cyclophosphamide were considered to have less frequent and shorter episodes than the placebo group and the trial sustained the belief that the beneficial effects of cyclophosphamide could be maximized and the adverse effects could be reduced using pulsed therapy (Killian *et al* 1988).

The Kaiser study (Likosky *et al* 1991) examined the efficacy of pulsed intensive immunosuppression with intravenous cyclophosphamide (c.500 mg/day until the leucocyte count reached $<4000/mm^3$) given in an outpatient setting under randomized single-blind conditions with folic acid as the comparator. At 1 year, 14 of 22 (64%) immunosuppressed patients were unchanged or stable compared to 14 of 20 (70%) taking folic acid. At 2 years, the figures were nine of 19 (47%) and nine of 17 (53%), respectively. There was no change in the rate of disability at 1 year between groups and each had worsened by approximately 0.5 EDSS points. However, at 2 years, patients on folic acid were accumulating disability at a faster rate than immunosuppressed patients (+0.4, 95% CI 0.4–1.2: the corresponding figure for the ambulation index was +0.8, 95% CI 0.5–2.2). Throughout, the authors nicely understate these results showing wide confidence intervals, in marked contrast to some other enthusiasts for the use of cyclophosphamide.

The definitive clinical trial of cyclophosphamide involved 168 patients (Canadian Co-operative Multiple Sclerosis Study Group 1991). Participants had progressive multiple sclerosis which had deteriorated by >1 EDSS point in the previous year. The proportions showing sustained deterioration of a further point (or more) were 35%, 32% and 29% in three groups – given intravenous cyclophosphamide with oral prednisolone, daily oral cyclophosphamide with alternate day prednisolone and weekly plasma exchange, or placebo preparations of all these treatments, respectively. There were no differences between groups in the proportions who improved, stabilized or worsened, nor in the final EDSS scores (Figure 18.6). Despite the necessarily complicated trial design, failure to demonstrate a difference in the overall outcome or interim assessments between groups was conclusive with respect to cyclophosphamide, not least because the study involved nearly three-fold more patients than earlier evaluations. However, perhaps the conclusion that 'immunosuppressive treatments do not stabilize or improve the clinical course in patients with multiple sclerosis' was overstated. Our position is that physician blinding prevented an erroneous conclusion being reached about the efficacy of intravenous cyclophosphamide in the Canadian study since Noseworthy *et al* (1994) point out that a treatment effect would have been reported (for the 6, 12 and 24 month epochs) had the analysis been based on the scores of neurologists who were unblinded during the trial and not (as was the case) the masked investigator. This analysis demonstrates, as well as any in the literature, the importance of evaluator blinding in the assessment of a putative treatment effect.

Although the Canadian study offered cyclophosphamide little future prospect as a treatment for multiple sclerosis, new studies have continued to appear. Weiner *et al* (1993a) extended their previous assessment of intravenous cyclophosphamide, modifying the induction regimen and adding so-called 'boosters' to maintain the effects. This required a comparison of four treatment groups but there was no difference in outcome between the two methods of induction. A higher proportion of patients who received further treatments with intravenous cyclophosphamide

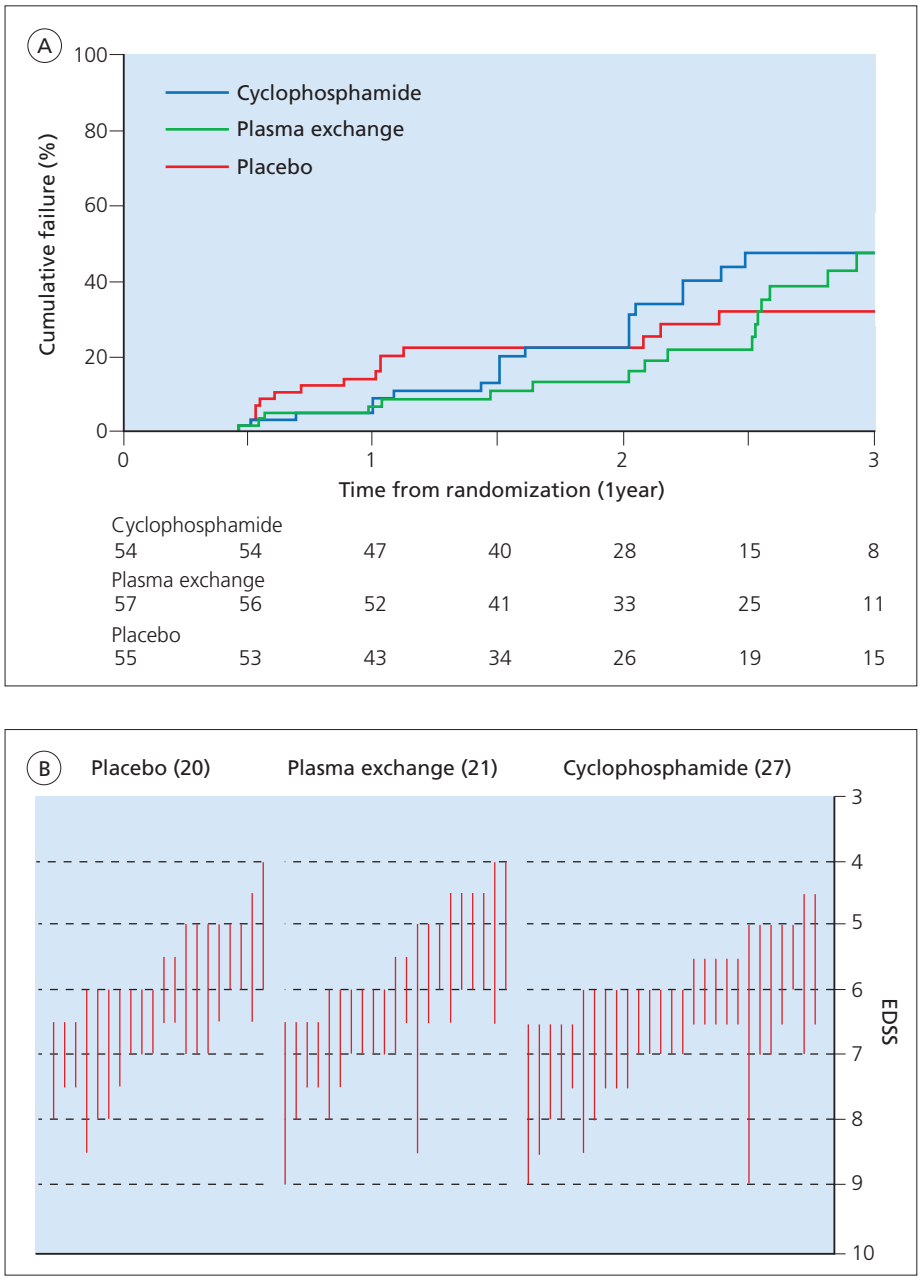


Figure 18.6 Canadian cyclophosphamide trial. (A) Time to treatment failure. (B) Extent of deterioration in EDSS. Every patient whose EDSS increased by >1 point (evaluating neurologist's assessment) at any one time during the trial is represented by a line connecting the EDSS at entry with the worst EDSS recorded during the trial. Numbers in parentheses are the numbers in each group who showed an increase of at least 1 EDSS point. Adapted from the Canadian Co-operative Multiple Sclerosis Study Group (1991). © 1991, with permission from Elsevier.

every 2 months for 2 years was clinically stable or improved at 24 and 30 (but not 6, 12 and 18) months and the time to treatment failure was prolonged in these two groups. Thirty-eight per cent responded clinically at 24 months in the two groups receiving boosters compared with 24% in the induction-only groups. Comparable figures at 30 months were 27% and 17%, respectively (Figure 18.7).

Weiner *et al* (1993a) emphasize that these clinical effects (which we consider to be modest and achieved at some price in terms of risk and potential adverse effects) are more likely to occur in young patients (aged <40 years) and not in individuals with primary progressive multiple sclerosis. In another report from this group, Gauthier *et al* (2003) reported a retrospective analysis of their experience using cyclophosphamide in 47 relapsing–remitting patients with multiple sclerosis considered unresponsive to glatiramer acetate and the various forms of IFN-β. The combination of pulsed intravenous methylprednisolone and cyclophosphamide appeared to stabilize MRI and clinical measures of progression in up to 75% of cases.

There have been no recent, randomized, controlled trials using cyclophosphamide but several investigators have reported apparently positive clinical experience. Based on an open label series of 17 patients with advanced disability (EDSS 6.0–8.5), who had deteriorated by at least 1.5 EDSS points despite recent treatment with corticosteroids, Weinstock-Guttman *et al* (1997) consider that high-dose intravenous cyclophosphamide and methylprednisolone followed by IFN-β therapy may stabilize rapidly worsening multiple sclerosis. They administered intravenous cyclophosphamide 500 mg/m^2 and 1.0 g intravenous methylprednisolone daily for 5 days along with abundant intravenous fluids to reduce the risk of haemorrhagic cystitis. Patients were then given a tapering course of oral prednisone for 12 days.

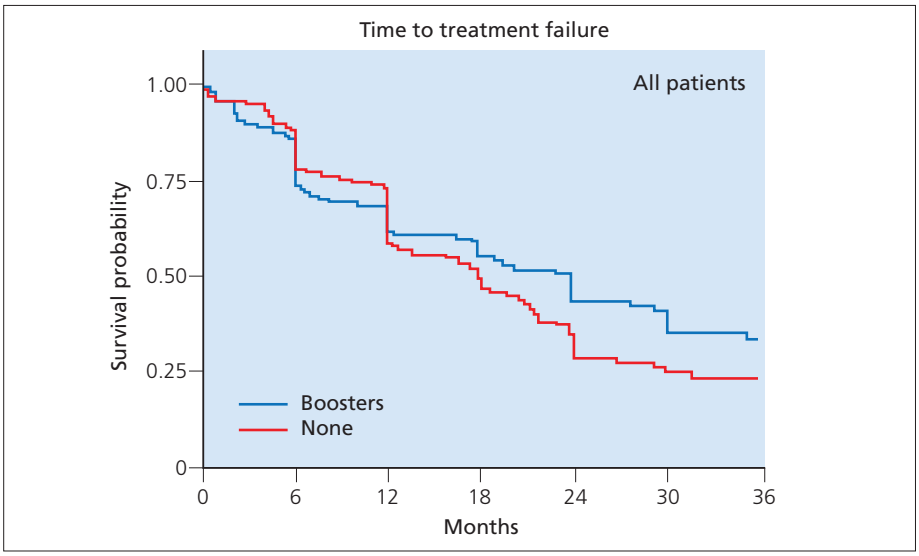


Figure 18.7 Kaplan–Meier survival curves comparing time to treatment failure in patients receiving and not receiving bimonthly cyclophosphamide booster therapy. Percentages of individuals who were not treatment failures are plotted against time. No significant difference was found ($p = 0.18$) over the entire course of follow-up, but in examining booster effects starting at 1 year, a significant benefit ($p = 0.03$) was detected. Adapted from Weiner *et al* (1993a). © 1993, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

Thereafter, 'maintenance immunotherapy' was continued at the discretion of the prescribing physician. This varied from repeated bimonthly treatments with intravenous cyclophosphamide and methylprednisolone, to weekly methotrexate or bimonthly intravenous methylprednisolone, and IFN-β1b. They reported that this complex immunological regimen was well tolerated (one patient had fever and two developed severe nausea and vomiting). Thirteen of 17 were either stable or improved at 1 year, and nine of 13 at 2 years. Although encouraging, collective experience has shown that nonrandomized, uncontrolled studies are often not validated by prospective studies using rigorous trial designs. In addition, the extreme variability of the 'maintenance immunotherapy' given to these patients leaves open too many freedoms in concluding what has and has not contributed to the complex equation of efficacy and clinical cost. Hohol *et al* (1999) reported their consecutive series of 95 patients with progressive forms of relapsing–remitting, secondary progressive and primary progressive multiple sclerosis. Each patient received 5 days of 1 g intravenous methylprednisolone followed on day 4 or 5 by a single course of intravenous cyclophosphamide (800 mg/m^2). Thereafter, patients received repeated single courses of 1 g intravenous methylprednisolone and cyclophosphamide (monthly dose increasing as needed to induce a mid-month leukopenia of 1500–2000 cells/mm^3). Patients were treated monthly for 1 year, every 6 weeks in year 2, and then every 8 weeks in year 3. This approach appeared most beneficial for patients with relatively recent onset secondary progressive multiple sclerosis (mean 2.1 years) whereas those with primary progressive disease responded less well. The authors reported that, at 2 years, 76% of the chronic progressive patients were stable or had improved using EDSS criteria. However, when using a combined outcome of either EDSS change or the examining physician's global impression of worsening, 54% of the patients with chronic progressive disease were judged to have deteriorated at 2 years.This experience is again unblinded and uncontrolled. Perhaps of equal importance, 70 of 95 patients discontinued the planned protocol prior to analysis, with approximately an equal number dropping out during each of the 3 years of follow-up. The authors conclude, as have many others, that the yield from treating secondary progressive multiple sclerosis using intensive immunosuppression diminishes with time. Gobbini *et al* (1999) administered high-dose pulse intravenous cyclophosphamide monthly for 6 months in a hospital setting to five patients with relapsing–remitting disease judged to have failed licensed therapies. Patients were adequately hydrated and underwent a 24 hour bladder irrigation protocol to reduce the likelihood of haemorrhagic cystitis. Cyclophosphamide was administered as 1 g/m^2 monthly with dose adjustments as needed to achieve a peripheral white blood cell count nadir of 1500–2000 cells/mm^3 at 10 days. Ondansetron hydrochloride 10 mg by intravenous injection was used to reduce nausea and vomiting. Monthly MRI studies demonstrated that all patients had a reduced number of gadolinium enhancing lesions by month five and two patients demonstrated a reduced T_2 lesion load. Two others could not be evaluated because of inadequate MRI. One patient continued to demonstrate an increase in T_2 lesion load despite stabilization of contrast enhancing lesions. One patient developed alopecia, another developed herpes zoster and, in two patients, a seizure disorder was observed but attributed to advanced multiple sclerosis. The authors conclude that this approach may be useful in patients failing approved therapies.

Monthly pulses of intravenous cyclophosphamide were used by S. Khan *et al* (2001a) in 14 patients with 'rapidly deteriorating' relapsing–remitting multiple sclerosis. Each had worsened by at least 3.0 EDSS points in the preceding year despite at least 6 months of an approved immune-modulating parenteral therapy and at least two courses of intravenous methylprednisolone. They administered 1 g/m^2 cyclophosphamide by monthly intravenous infusion, adjusting the dose based on a target peripheral white blood cell nadir of 2000–2200 cells/mm^3 at 14 days. Most patients were treated for 6 months and then started on one of the approved therapies. Dexamethasone (20 mg) and ondansetron (32 mg, each by intravenous injection) were administered, along with intravenous fluids to prevent haemorrhagic cystitis. All patients were thought to have stabilized or improved by 6 months and this apparent clinical benefit persisted for an additional year (assessed at 18 months, postinduction). Mild or moderate nausea and transient alopecia were reported but no participant experienced haemorrhagic cystitis or clinical relapses. Self-evidently, cyclophosphamide is a complicated drug to administer and the

net contribution to the welfare of people with multiple sclerosis is hard to evaluate. For example, in a comparative study of patients receiving monthly infusions of methylprednisolone (n = 15), bimonthly intravenous cyclophosphamide with methylprednisolone (n = 32), methotrexate (n = 5) or IFN-β (n = 15), there was early and sustained selective increase in eosinophilia and raised levels of stimulated CD4 T-cell-secreted IL-4 and IL-10 with a reduction in production of IFN-γ in the cyclophosphamide group – representing both inhibition and enhancement of potentially immunopathogenic processes – not seen with the other putative therapeutic agents (D.R. Smith *et al* 1997). A recent Cochrane systematic review concluded that cyclophosphamide does not prevent worsening of the EDSS but appears favourably to influence the rate of EDSS change at 12–18 months (La Mantia *et al* 2002). Astonishingly, only four randomized trials from a total of 326 published reports were judged suitable for review because of limitations in trial design and conduct. These authors cautioned against the use of this agent because of the frequency of sepsis and amenorrhoea in treated patients.

We rarely, if ever, use cyclophosphamide in our clinical practice. It may be that this powerful immunosuppressive agent has a role in stabilizing patients with very active disease but our reading of the published reports suggests extreme caution. As in many trials where the first reported effect has not been confirmed, the treated group fared no better than patients receiving placebo but nonetheless participating in trials of chronic progressive multiple sclerosis. This calls to mind the remark of the late Dale McFarlin:

> *when I get multiple sclerosis, put me in a trial and make sure I get the placebo.*

Plasma exchange

Plasma exchange has been used in patients with multiple sclerosis in the hope of matching the uncomplicated benefits achieved in other inflammatory disorders. It has been evaluated both as a disease-modifying agent and in the management of refractory acute episodes (see Chapter 16). Although the mode of action in disorders where details of the immunopathogenesis remain to be fully characterized is obscure, plasma exchange presumably removes or indirectly restores to balance soluble mediators of immunity. The same general principle is thought to underlie the use of immune globulin (see below).

Khatri *et al* (1991) reviewed their experience of plasma exchange in 200 patients with progressive multiple sclerosis (based on a recent retrospective review of case records) also receiving cyclophosphamide, prednisolone and symptomatic treatments. Pooled human globulin was used to replace fluid after exchanges given weekly for 3 months with a subsequent weaning period, the duration of which depended on initial response. The results showed a reduction in EDSS at 1, 2 and 3 years by comparison with scores at entry, and the authors considered that >80% of patients had improved or stabilized by 3 years. Four potentially active treatments were used in the study. Patients were selected on the basis of ability to pay for therapy through insurance. There were no controls. It is therefore difficult to reach any conclusions from this evidence on whether plasma exchange has an independent effect, complements immunosuppressants or makes no contribution to the management of disease progression. Whereas the Canadian Cooperative Multiple Sclerosis Study Group (1991) concluded on the basis of their study that immunosuppressants (then available) were generally ineffective in multiple sclerosis, Khatri *et al* (1991) reached diametrically opposite conclusions using a comparable regimen of combined therapies.

Most reported studies use plasma exchange as an adjunct to other forms of immunological treatment. Thus, the clinical course has been shown to stabilize in patients with progressive disease treated with corticosteroids and cyclophosphamide, whether or not plasma exchange is also used (Khatri *et al* 1985). An earlier trial comparing plasma exchange in patients also receiving azathioprine showed that both groups deteriorated at a comparable rate (Tindall *et al* 1982). Confirming that the short-term consequences of relapse are reversed more rapidly in patients receiving plasma exchange in addition to intramuscular corticotropin and cyclophosphamide, Weiner *et al* (1989) were unable to demonstrate any long-term effects. The contribution made by plasma exchange in patients also receiving azathioprine was assessed in a crossover design by P.S. Sorensen *et al* (1996). Fourteen exchanges were given over 20 weeks in the active period. Plasmapheresis had no effect on disease activity as assessed by gadolinium enhanced MRI, although the total lesion load and central motor conduction times were reduced during the exchange period. A specific role for plasma exchange in the treatment of fulminant demyelination was reported by M. Rodriguez *et al* (1993a). This observation is substantiated by both a randomized, double-blinded trial (Weinshenker *et al* 1999b) and an uncontrolled, prospective series (Keegan *et al* 2002) of patients who failed to improve following a course of steroid treatment in the setting of acute inflammatory demyelination because of established multiple sclerosis, neuromyelitis optica or a first episode of demyelinating disease. Bringing together empirical observations treating fulminating episodes of demyelination with plasma exchange and histological observations made in the highly selected group of cases studied by brain biopsy, Keegan *et al* (2005) subsequently correlated the presence of antibody and complement deposition (type 2: see Chapter 12) with moderate to substantial functional improvement – responses that were not seen in patients with other histological features. It remains unclear at what point in the natural history of an episode with poor recovery, plasma exchange might be considered as one option for limiting the extent of persistent or long-term disability, thereby constituting a disease-modifying treatment (see Chapter 16).

Intravenous immunoglobulin

We refer elsewhere (see below, and Chapters 10 and 19) to the potential for remyelination from the use of intravenous immunoglobulin in experimental demyelination and the clinical setting. Intravenous immunoglobulins are widely used in the management of peripheral and central nervous system disorders (Wiles *et al* 2002). Intravenous immunoglobulin has been assessed in detail for a variety of indications in multiple sclerosis (Stangel and Hartung 2002), including attempts to alter the natural history of relapsing–remitting and secondary progressive disease, and to reverse established deficits by enhancing remyelination (Asakura 1996; Rodriguez and Lennon 1990; M. Rodriguez *et al*

1996). Immunoglobulins may stimulate remyelination in the Theiler's murine encephalomyelitis virus animal model. Other possible mechanisms of action include an effect on anti-idiotypes (Tenser *et al* 1993), interference with complement (M.M. Frank *et al* 1992) or Fc-receptor-mediated interactions between microglia and their opsonized targets (Jungi *et al* 1990), or a reduction in cytokine production (U.G. Anderson *et al* 1993). Whatever the mode of action, intravenous immunoglobulin appears to be safe and generally well tolerated.

Schuller and Govaerts (1983) first used immune globulin in multiple sclerosis, reporting that 11 of 31 patients with chronic progressive disease showed improvement. Nine were unchanged and the remaining 11 deteriorated. These results are rather reminiscent of the rule of thirds in multiple sclerosis treatment trials (one-third each better, same and worse). Achiron *et al* (1992b) later reported an open controlled trial using 0.4 g/kg intravenous immunoglobulin given for 5 days and then every 2 months for 1 year in ten patients and ten controls. Treatment was well tolerated. Relapse rate changed in the treated group from 3.7 (± 1.2)/year to 1.0 (± 0.7)/year, and from 3.3 (± 1.4)/year to 3.0 (± 1.6)/year in controls (which is rather high for unselected patients). At 12 months, the EDSS had changed from 4.5 to 4.2 in treated patients and from 3.5 to 3.7 in controls. Cook *et al* (1992) combined intravenous immunoglobulin (0.5–2 g/kg) with methylprednisolone given monthly to 14 patients with progressive multiple sclerosis. These were unusual in that 11 of the patients were considered to be corticosteroid dependent. During follow-up (mean duration 7.8 months) 11 patients experienced 17 relapses, many of which occurred within 1 month of treatment or coincided with attempts to taper the dose of corticosteroids. Tenser *et al* (1993) treated six patients with relapsing progressive multiple sclerosis for 2 days with 0.8 g/kg of intravenous immunoglobulin. Whilst we question the value of learning that two of them felt better, the main purpose of this study was to demonstrate immunological effects on immune function. van Engelen *et al* (1992) treated five patients with stable visual deficits, in the context of multiple sclerosis which had not previously responded to intravenous methylprednisolone, with 0.4 g/kg intravenous immunoglobulin for 5 days followed by a single dose twice monthly for 3 months. Vision started to improve within 12 months of treatment and was maintained for >1 year, but this did not correlate closely with psychophysical tests or imaging appearances.

Fazekas *et al* (1997) randomized a larger group (150 patients with relapsing multiple sclerosis having clinical evidence for moderate but neither trivial nor severe disability and without chronic progression) to a single monthly infusion of intravenous immunoglobulin (0.15–0.2 g/kg). This is a low dose. Exposure to other forms of immunosuppression up to 3 months (2 weeks for corticosteroids) previously was permitted, as was methylprednisolone in pulses of up to 10 g during intercurrent relapses. This design limits the confidence with which the otherwise impressive and statistically significant effects on disability (the primary outcome measure) and relapse activity can be assessed. In an intention to treat analysis, the proportions improving, worsening or unchanged in the treated group were 31%, 16% and 53% compared with 14%, 23% and 63% in placebo patients, respectively. However, the magnitude of change was small, being –0.2 EDSS points in treated patients and +0.1 in the placebo group (a difference of 0.3; $p = 0.008$). The effect on relapse frequency shows the now familiar pattern. Treated patients had a reduction in baseline rate from 1.3 to 0.5 relapses during the first year (a reduction of 0.8 per year), which stabilized at 0.4 per annum in the second year compared with baseline, 1 year and 2 year rates of 1.4, 1.3 and 0.8 (reductions of 0.1 and 0.5, respectively) in the placebo group. Thus, the impact was all in the first year. Adverse effects were few and probably unrelated to medication. On closer inspection, however, a couple of additional points should be mentioned. Surprisingly, less reduction in relapse rate was seen in the placebo group than is usual in comparable trials. We wonder whether blinding was adequate. Failure of regression to the mean in the control group may have inflated the apparent treatment benefit. Investigators did not require a second confirmatory examination to determine that the apparent delay in EDSS progression was sustained at further examinations separated by 3, 6 or 12 months. The effect of intravenous immunoglobulin on MRI behaviour was not assessed in this study. However, in a small study, G.S. Francis *et al* (1997) demonstrated that intravenous immunoglobulin had no apparent effect on MRI behaviour in nine patients given induction and monthly booster doses. They continued to relapse, progress and accumulate T_2-weighted MRI lesions.

Achiron *et al* (1998) randomized 40 patients to induction and maintenance treatment with intravenous immunoglobulin (0.4 g/kg for 5 days with a single treatment every 2 months for 2 years) or placebo. Primary outcome measures related to relapse frequency, interval, time to next episode, and severity. These were patients with high pretreatment relapse rates and, unusually, the placebo cases showed fluctuations in relapse rate (1.5, 1.8 and 1.4 per year before and during each of the 3 years of the study, respectively), whereas treated patients showed a reduction (1.8, 0.7 and 0.4 per year, respectively; $p = 0.0006$, overall). Annual change in relapse rate across the 3 years of observation was –1.1 and –0.3 in patients receiving intravenous immunoglobulin compared with +0.2 and –0.4 in the placebo group. Thus, the effect on relapse rate depended entirely on the first year effect during which treated patients improved and the placebo group deteriorated (a difference in activity of 1.4 relapses/year). A greater proportion of treated patients (six of 20) than controls (none of 20) remained exacerbation free during the entire period of the study, and the time to first relapse was longer (233 compared with 82 days). There was no difference in mean EDSS scores between groups but a favourable distribution in the proportion within each group who worsened, improved or remained stable (14%, 24% and 63% in those receiving immunoglobulin compared with 17%, 11% and 72% in the placebo group, respectively) was observed. The protocol for MRI does not allow useful conclusions to be drawn. Twenty-six patients were treated by P.S. Sorensen *et al* (1998) in a crossover design with intravenous immunoglobulin 2 g/kg or placebo monthly each for 6 months. There were fewer new enhancing lesions on MRI (the primary end point; however, no benefit was seen in the number of new T_2 lesions) and a greater proportion of patients was relapse free (the secondary outcome) during periods of active therapy. Although promising, these smaller studies all failed to reproduce the original claim of Fazekas *et al* (1997). Consequently, intravenous immunoglobulin is not widely used as maintenance therapy to reduce relapse frequency in relapsing–remitting multiple sclerosis but, rather, is considered a second-line therapy (Rieckmann and Toyka 1999).

In a preliminary study involving 108 pregnancies, Achiron *et al* (2004b) investigated the specific issue of reducing the possibility of disease activity – manifesting as new relapses – in the puerperium by prophylactic use of intravenous immunoglobulin. Two treatment groups (intravenous immunoglobulin 0.4 g/kg/day for 5 consecutive days in week one after delivery with the same regimen at weeks six and twelve after delivery; or 0.4 g/kg/day for 5 consecutive days within 8 weeks of conception, and once every 6 weeks until 12 weeks postpartum) were compared with untreated mothers. No confounding factors were identified and there were no serious adverse events. The group treated during pregnancy showed fewer relapses during pregnancy (0.43, 0.15 and 0.0 annualized rates for each trimester compared with 0.72, 0.61 and 0.41 in controls); both treated groups had fewer episodes in the puerperium (0.28 and 0.58 annualized rates, respectively) compared with controls (1.33). This initial study suggests that further controlled trials of intravenous immunoglobulin in this clinical setting are needed.

A recently completed phase three study of intravenous immunoglobulin in secondary progressive multiple sclerosis involved 318 patients randomized to receive monthly infusions of either intravenous immunoglobulin 10% at a dose of 1 g/kg body weight (to a maximum of 80 g; eight vials) or the same volume of placebo with 0.1 g albumin per vial. Although there was a treatment advantage over the first year of the trial, this benefit was soon lost since treatment did not influence the proportion of patients classified as treatment failures (confirmed progression of EDSS of 1.0, or 0.5 for baseline EDSS of ≥ 6.0), or reduce MRI evidence of T_2 lesion accumulation. The trial was stopped after 27 months based on this interim analysis demonstrating futility (Hommes *et al* 2004). Of interest, however, was a reported beneficial effect on the development of brain atrophy (Lin *et al* 2002).

Following one clinical report that intravenous immunoglobulin might benefit patients with longstanding visual loss due to multiple sclerosis (van Engelen *et al* 1992), Noseworthy *et al* (2000b; 2001) conducted two randomized, double-blinded, placebo-controlled phase two trials to determine if intravenous immunoglobulin might restore function in the setting of persistent (visual) clinical deficits. In the first study, 67 patients with either relapsing–remitting (n = 19) or secondary progressive multiple sclerosis (n = 48), known to have a moderately severe fixed motor deficit (confirmed by isometric biomechanical muscle strength testing), were randomized to receive either 0.4 g/kg intravenous immunoglobulin daily for 5 days then every 2 weeks for 3 months (representing a total of 11 infusions) or placebo. Treatment failed to demonstrate an improvement in strength of the targeted muscle groups or benefits in any secondary outcome measures. In the second study, 55 patients with persistent visual loss from inflammatory optic neuritis were randomized to receive either 0.4 g/kg intravenous immunoglobulin daily for 5 days then monthly for 3 months (a total of eight infusions) or placebo. Treatment did not improve the primary visual outcomes (visual log acuity scores at 6 months) and the trial was again stopped on the futility principle. Stangel *et al* (2000a) were also unable to demonstrate that treatment with either placebo or intravenous immunoglobulin (0.4 g/kg/day for 5 days) separated by 6 weeks improved central conduction motor conduction velocity in ten patients with multiple sclerosis.

In summary, there is only limited evidence to support a role for intravenous immunoglobulin in patients with demyelinating disease of the central nervous system (other than those who have failed to respond to high-dose steroids or plasma exchange in the setting of a catastrophic relapse; see above and Chapter 16). Future randomized studies may change this recommendation.

Methotrexate

Despite being available for many years, methotrexate has only recently been evaluated in multiple sclerosis. The first study (J.W. Neumann and Ziegler 1972) alternated treatment with methotrexate (2.5 mg/day) and 6-mercaptopurine (75 mg/day) in 3-monthly cycles. There was no clinical effect but the study design was not ideal. Subsequently, Currier *et al* (1993) reported a reduction in relapse rate for patients in the relapsing–remitting phase treated with methotrexate but there was no effect on disability in patients with progressive multiple sclerosis. The role of methotrexate in this clinical situation was specifically assessed by D.E. Goodkin *et al* (1995). Sixty patients with secondary or primary progressive disease were randomized to treatment with a weekly oral dose of 7.5 mg methotrexate or placebo. Methotrexate was well tolerated and the relative absence of adverse effects allowed blinding to be maintained throughout the study. Overall, patients and independent observers were unimpressed by the results. Objective assessments, using a complex composite scale which independently assessed the EDSS, ambulation index, box and block and nine-hole peg tests (upper limb function), and new or enlarging MRI lesions, showed a statistically significant effect of methotrexate on function in the peg test but not the box and block method for assessing upper limb function or mobility.

Subsequently, D.E. Goodkin *et al* (1996) reported on changes in active MRI lesions and T_2-weighted total lesion load but, by comparison with other claims for an effect on surrogate markers of disease activity, methotrexate was relatively unimpressive. In correspondence, Olek *et al* (1996) indicated that weekly subcutaneous injections of a higher dose (20 mg) of methotrexate were generally well tolerated by 38 patients although one developed an injection site abscess and transient liver enzyme elevation was occasionally seen. The full report of this study appears not to have been published.

In a preliminary trial of 15 patients, Calabresi *et al* (2002b) showed that, when added to weekly IFN-β1a, methotrexate 20 mg orally, also in a single dose each week, seemed to reduce gadolinium enhancements and may have provided an additional protection against relapses. In a very small study, Rowe *et al* (2003) reported preliminary findings from adding high-dose intravenous methotrexate (2 g/m^2) every 2 months for 1 year in 15 patients with relapsing–remitting multiple sclerosis who had demonstrated neurological worsening during the preceding period on IFN-β1a weekly by intramuscular injection. Patients continued on weekly IFN-β1a tolerated combination therapy with evidence for stabilization of the clinical course as judged by the MSFC (see above), and with immunological markers suggesting an influence on disease mechanisms. We understand that a four-arm trial designed to determine whether methotrexate (20 mg orally per week) alone or in combination with methylprednisolone (1000 mg by intravenous infusion for 3 days every 2 months) provides a treatment advantage over weekly IFN-β1a in 900 patients with relapsing–remitting multiple sclerosis who have failed interferon alone is in progress. However, despite

these ongoing studies, at present methotrexate joins cyclophosphamide and azathioprine as medications rarely, if ever, prescribed in our clinical practice.

Mitoxantrone

Mitoxantrone is an anthracenedione antineoplastic agent that intercalates with DNA and inhibits both DNA and RNA synthesis, suppressing T-cell and B-cell immunity. Mauch *et al* (1992) first treated 12 patients perceived to have rapid progression of disability with mitoxantrone (12 mg/m^2). All reported clinical stabilization and eight of them were considered to have improved at 1 year. The patients had 169 gadolinium-DTPA enhancing lesions at entry but only 10 were visible on completion of the study. Adverse effects were minimal. Mitoxantrone was next assessed in a small open study involving 13 patients with progressive multiple sclerosis (Noseworthy *et al* 1993). Participants received seven intravenous infusions over 3 weeks. Nine of the 13 patients had been observed over the previous 18 months and, in the remainder, historical evidence for rate of progression was available from case records. Initially, the clinical course appeared to stabilize and no changes in EDSS were seen for up to 12 months, but progression was apparent 6 months later. Although the authors considered progression to have occurred at a slower rate than expected from pretreatment observations in this cohort of patients, the changes were consistent with the natural history of multiple sclerosis previously seen in their placebo-controlled study of cyclophosphamide (see above). In eight of the 12 patients, there was evidence for continuing MRI activity during treatment with mitoxantrone.

In a subsequent study (Edan *et al* 1997), 42 patients with aggressive active clinical and radiological disease all receiving monthly injections of methylprednisolone were randomized to 6 months of treatment with intravenous mitoxantrone (20 mg/month) or no additional therapy. The baseline relapse rate was three per year in those who met the radiological guidelines for inclusion (there had to be gadolinium enhancing lesions) compared with 0.7 per year in patients who reported attacks in advance of selection but did not meet the radiological criteria for inclusion. Mitoxantrone was associated with a significantly higher frequency of conversion to disease inactivity as judged by gadolinium enhanced MRI activity. The mean number of enhancing lesions was reduced by about 90%, similar to that seen with other aggressive immunosuppressive regimens. Although both the number of participants and duration of follow-up prevented detailed assessment, there was an apparent beneficial effect of treatment on relapse rate and disability. The profile of adverse effects inhibited blinding, but no serious consequences of treatment were observed. In a 1 year study aimed at demonstrating whether mitoxantrone is cardiotoxic, De Castro *et al* (1995) showed a reduction in relapse rate in treated patients. There were no electrocardiographic or echocardiographic abnormalities. Millefiorini *et al* (1997) treated 27 patients monthly for 1 year with intravenous mitoxantrone (8 mg/m^2) or placebo. The differences in rate of accumulation of disability and number of relapses favoured a treatment effect. Nine of 24 placebo-treated patients deteriorated by up to 1 point on the EDSS compared with two of 27 patients given mitoxantrone. Five of 24 from the placebo group were free from exacerbations during the trial compared with 17 of the 27 patients given mitoxantrone. This was reasonably well tolerated and, again, with no cardiac toxicity. However, MRI did not show a significant reduction in disease activity and, in this respect, the results provide less persuasive evidence for the therapeutic role of mitoxantrone than those reported by Edan *et al* (1997).

After a 4 year interval between the initial declaration of results in abstract form and full publication, Hartung *et al* (2002) reported on MIMS (Mitoxantrone in MS Study Group). In this double-blind, placebo-controlled, multicentre study (17 centres in four European countries: Germany, Belgium, Hungary and Poland), MIMS randomized 194 patients with either worsening relapsing–remitting (progressive relapsing) or secondary progressive multiple sclerosis to treatment either with placebo (3 mg methylene blue) or mitoxantrone (5 or 12 mg/m^2 intravenously every 12 weeks for 24 months). Inclusion criteria required that patients had deteriorated by up to 1.0 EDSS point in the 18 months prior to enrolment with a baseline EDSS of 3.0–6.0. Annual MRI scans were performed on a subset of 110 patients. The primary outcome measure was a composite score comprised of five clinical measures: change in EDSS at 2 years; change in ambulation index at 2 years; change in the baseline standardized neurological status at 2 years; number of relapses requiring corticosteroid treatment; and time to first relapse. Seventy-seven per cent completed 24 months of follow-up (71% completed 36 months in the study). Those who discontinued treatment were slightly more common in the control group. At 24 months, benefit was reported in all five components of the composite measure for both active treatment arms, with the overall greatest benefit noted between placebo and the group receiving mitoxantrone at a dose of 12 mg/m^2 ($p < 0.0001$: Figure 18.8). That said, the magnitude of the effect on EDSS was rather modest [essentially mild benefit vs. mild deterioration; mean EDSS change for high-dose mitoxantrone, –0.13 (SD 0.90) vs. +0.23 (SD 1.01) in the placebo group] as expected in a trial of relatively brief duration. Preliminary MRI analysis also indicated a treatment effect with fewer T_2-weighted lesions and fewer patients experiencing enhancing lesions at 2 years in the high-dose group (see below). Post hoc analysis was performed

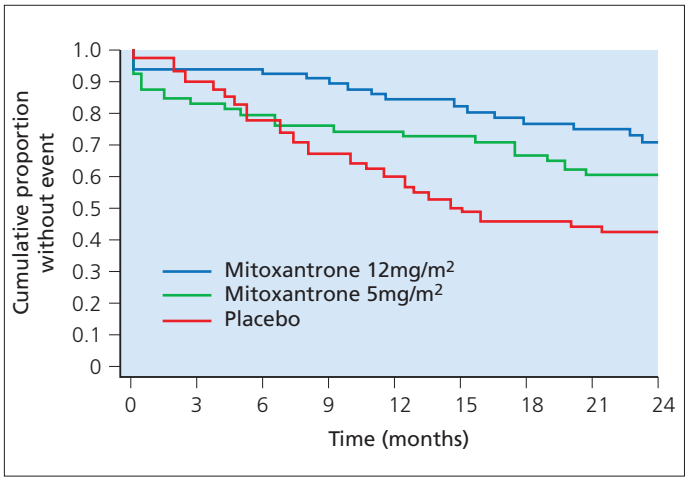


Figure 18.8 Treatment of progressive multiple sclerosis with mitoxantrone. Time to first relapse. Both doses of mitoxantrone delayed time to first recorded relapse by the treating physician. This individual was aware of the treatment assignment. Adapted from Hartung *et al* (2002). © 2002, with permission from Elsevier.

based on the 18-month pre-enrolment relapse history, to determine whether mitoxantrone was equally effective in patients with ongoing relapses and those progressing with superimposed relapses. This subgroup analysis was underpowered but showed a similar benefit in both groups of patients. However, there was a trend for EDSS progression in all relapse-free patients irrespective of treatment assignment, albeit to a lesser degree in those who received mitoxantrone. Indeed, the mean EDSS worsening at 2 years in previously relapse-free mitoxantrone recipients was virtually the same as that seen in the placebo-treated relapsing patients.

A few points merit additional comment. This study generated widespread use of mitoxantrone in patients failing to respond to the interferons and glatiramer acetate (K.K. Jain 2000). It contributed to the Food and Drug Administration (FDA; United States) approval of mitoxantrone for use in progressive multiple sclerosis even though a peer-reviewed manuscript was not published for a further 2 years. This delay remains unexplained. Additionally, the detailed MRI analysis is still not available. With respect to design and conduct of the study, an unblinded physician was used to determine relapse status. Success of the blinding procedure was not assessed. Nausea and mild alopecia were reported but tolerated. Secondary amenorrhoea lasting at least 1 year developed in 25% of women receiving high-dose mitoxantrone. No patients developed significant cardiomyopathy. Goodin *et al* (2003) recently highlighted an important concern that re-analysis by the sponsor (Immunex) with selective censoring of the treatment arms contributed to the reported treatment and its magnitude. Goodin *et al* (2003) point out that, at 3 years, the benefit in standardized neurological status persisted but the EDSS and ambulation index results did not. They question whether methylene blue may have been neurotoxic and thereby contributed to the clinical and MRI decline in control patients. They also emphasize that high-dose mitoxantrone did not affect the mean number of gadolinium enhancing lesions ($p = 0.1$). The apparent effect of low-dose mitoxantrone was not subjected to statistical analysis. High-dose mitoxantrone reduced T_2 number ($p = 0.03$) and the number of new contrast enhancing lesions ($p = 0.02$) but there was no apparent effect on T_2 lesion load.

Taken together, the limited evidence to date supports the conclusion that mitoxantrone reduces relapse frequency and MRI evidence for blood–brain barrier disruption in patients with very active multiple sclerosis. The benefit for patients with relapse-independent progression is less certain. The recently published report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Goodin *et al* 2003) recommends caution in the use of this drug, and calls for confirmatory studies. We recommend this report as a balanced and comprehensive review of the evidence for efficacy and the range of toxicity associated with the use of mitoxantrone in multiple sclerosis. The magnitude of the expected treatment effect is perhaps best stated using the 'numbers needed to treat (NNT)' approach (Sackett *et al* 2000). From the MIMS results, one would need to treat 11 patients with secondary progressive multiple sclerosis for 2 years to prevent one person from worsening by 1.0 EDSS point.

Mitoxantrone is a toxic agent that must be administered with care to reduce the likelihood of marrow suppression, opportunistic infection and cardiomyopathy. Amenorrhoea is an important concern for many young women. The risk of cardiomyopathy is generally dose dependent and may be as great as 6% in cancer patients receiving up to 140 mg/m^2 (Dukart 1984; Mather 1987). In most trials involving patients with multiple sclerosis, and in our clinical practice, regular pretreatment echocardiograms can be used to screen for reduced left ventricular function. The MIMS investigators recommend measuring cardiac output at baseline and thereafter, once patients have received a total of 100 mg/m^2. In practice, we measure cardiac output before each infusion and discontinue mitoxantrone if there is evidence for a reduction. Irreversible cardiomyopathy requiring transplantation has been reported in patients with multiple sclerosis exposed to excessive doses of this agent. Pathological findings in such cases include noninflammatory myofilament rarefaction and degeneration, sarcoplasmic dilatation, and interstitial fibrosis (Gbadamosi 2003b). Goffette *et al* (2005) reported three cases of delayed cardiomyopathy (heart failure) beginning 24–80 months after the last dose of mitoxantrone (total cumulative dose 144 mg/m^2) with no adequate explanation other than prior treatment with cyclophosphamide (two patients). This report reminds us of the need to use caution in the decision to use this agent and to be rigorous in maintaining close follow-up thereafter. Mitoxantrone is a topoisomerase II inhibitor and therefore may predispose to treatment-related leukaemia. There are now several reports possibly linking mitoxantrone to the development of acute leukaemia (Brassat 2002; Cattaneo 2003; Mogenet *et al* 2003; A.M. Vicari 1998). In a review of the literature, Ghalie *et al* (2002) estimated the risk of therapy-related acute leukaemia in patients with multiple sclerosis receiving mitoxantrone at 0.05–0.1%. This perceived rate may be on the low side; by 2004, there were currently five examples of acute leukaemia amongst a register of 2336 patients with multiple sclerosis receiving mitoxantrone, representing a cumulative incidence of 0.21% (Voltz *et al* 2004).

In the United States, Novantrone (mitoxantrone) is licensed by the FDA for

> *reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e. patients whose neurologic status is significantly abnormal between relapses). Novantrone is not indicated in treatment of patients with primary progressive multiple sclerosis.*

In Europe, although unlicensed, mitoxantrone is not infrequently used to treat patients who are deteriorating along the lines described in the FDA licence. We use the drug sparingly, reserving mitoxantrone for patients who continue to suffer clinical and MRI evidence of active disease (frequent significant relapses and multiple contrast enhancements) despite treatment with interferons (or glatiramer acetate). In one of our centres (D.H.M.), it is required that there has been a deterioration of at least 2 EDSS points within 12 months, accompanied by evidence for active inflammatory disease based either on the occurrence of clinical relapses or the presence of gadolinium enhancing MRI lesions. We generally administer 12 mg/m^2 by intravenous infusion every 3 months for not more than eight cycles but hope for a stronger evidence base from ongoing trials resolving the issue of whether higher cumulative doses offer

increased efficacy but without increasing the risk. We sometimes use the protocol of Edan *et al* (1997), namely mitoxantrone 20 mg monthly by intravenous injection for 6 months, in the small group of patients with particularly aggressive fulminant disease, in whom rapidly increasing disability has accumulated on the basis of frequent, severe relapses and many active inflammatory lesions on gadolinium enhanced MRI.

Cladribine

Cladribine specifically induces apoptotic death in resting and dividing lymphocytes but is otherwise relatively nontoxic. After assessing safety and obtaining a preliminary impression of efficacy, Sipe *et al* (1994) compared monthly pulses of cladribine given by an indwelling intravenous line with placebo in 51 patients with progresssive multiple sclerosis. The analysis was confined to 48 participants randomized initially to receive cladribine or placebo, completing the assessment at 1 year. Of the three remaining patients, one died from acute hepatic failure, one withdrew after suffering a hip fracture and one was lost to follow-up. Three other treated patients had significant episodes of infection and there was evidence for bone marrow suppression in another, but these all continued in the study. This was terminated on the basis of results at 1 year without embarking on the planned crossover phase. Placebo-treated patients deteriorated by approximately 1 EDSS point and by a comparable amount on a locally designed neurological rating scale (the Scripps scale), whereas those receiving cladribine remained stable or showed modest clinical improvement in preexisting disabilities. The numbers of patients showing deterioration (by >1 EDSS point), improvement or stabilization were seven, one and 15 of the 23 patients in the placebo group compared with one, four and 19 of the 24 patients randomized to cladribine, respectively. Within pairs, a greater number showed no disease activity in serial MRI characteristics in the cladribine group compared with their placebo-treated partners (Figure 18.9A and B). There was some evidence for a difference in concentration, but not in the number, of oligoclonal bands in cladribine-treated patients compared with the placebo group. Since cladribine can now be given subcutaneously, the authors recommend its use at a lower dose than was evaluated in their trial of chronic progressive multiple sclerosis on the basis of efficacy and acceptable risks. Critics have argued that the original trial design was not strictly followed, and that the result was largely achieved through the atypical and severe course of the placebo group. However, in a preliminary communication, others have since endorsed the difference in natural history of progressive multiple sclerosis between patients receiving pulsed treatment with cladribine and placebo (Grieb *et al* 1994).

In a subsequent publication, Beutler *et al* (1996) extended the period of observation for the original study. Maintaining the blinded design, they crossed over the two randomized groups of patients, administering placebo to the original cladribine group and gave a reduced dose of cladribine to the patients who had first received placebo. A treatment effect was still claimed. The magnitude was reduced but toxicity was also less marked with the lower dose. The authors noted that cladribine can be given safely and with apparent equal efficacy by the subcutaneous route. Our position is that bone marrow toxicity (especially thrombocytopenia), herpetic infection in six patients and reported protocol violations undermine the likelihood that the trial was sufficiently blinded to be convincing.

There are several more recent reports exploring the potential use of cladribine in multiple sclerosis. Romine *et al* (1999) claimed clinical benefit, measured as a reduction in the combined outcome of relapse severity and frequency, in a short (18 month) double-blind, placebo-controlled trial of cladribine (0.07 mg/kg subcutaneously daily for 5 days and repeated monthly for 6 months; total 2.1 mg/kg) given to 52 patients with relapsing–remitting disease. Relapse rate fell dramatically during the first 6 months of the trial, especially in the placebo group but, thereafter, treated patients continued to show fewer episodes. Cladribine-treated patients also had fewer gadolinium enhancing MRI lesions. In a phase three trial involving patients with progressive multiple sclerosis, Rice *et al* (2000) demonstrated that each of two doses of cladribine (0.07 mg/kg subcutaneously daily for 5 days each month repeated for either 2 or 6 months) reduced MRI evidence of disease activity in the subset of patients with secondary progressive disease. Unfortunately, this trial was limited to 1 year of follow-up and no clinical benefit was apparent in the primary outcome measures (EDSS and Scripps Neurologic Rating Scale). Both doses reduced the number and volumes of contrast enhancing lesions. The higher dose also reduced T_2 lesion load. Significantly, there was no effect on the progression of cerebral atrophy (Filippi *et al* 2000a; 2000b). We remain to be convinced that cladribine is useful, and do not recommend its use in the management of patients with multiple sclerosis.

Sulfasalazine

Noseworthy *et al* (1998) conducted a phase three trial designed to determine whether prolonged administration of sulfasalazine might reduce disease activity in patients with active multiple sclerosis. The trial was started before completion of the first definitive trial of IFN-β and at a time when there were no approved therapies for multiple sclerosis. Sulfasalazine is a well-tolerated oral agent for which a number of relatively mild immunosuppressive activities had previously been claimed together with moderate efficacy in other chronic immune-mediated disorders including rheumatoid arthritis and inflammatory bowel disease. Interim analysis suggested that treatment had been mildly effective early in the trial. Wisely, the data monitoring committee recommended that the study be continued to completion – and the early benefits disappeared so that, in the final analysis, there was no overall benefit (Figure 18.10). The decision to continue this trial without informing the investigators or sponsors of the early apparent benefit, and the subsequent recognition that early effects are often transient, provides an important lesson for the design and conduct of treatment trials in multiple sclerosis that has subsequently been well learned. Thus, sulfasalazine joins the list of agents that do not have a role in the treatment of multiple sclerosis.

Corticosteroids

Despite the unambiguous evidence that corticosteroids hasten clinical recovery in the setting of acute relapse (see Chapter 16), it has previously been held as axiomatic that they have no effect on the natural history of multiple sclerosis. But until recently,

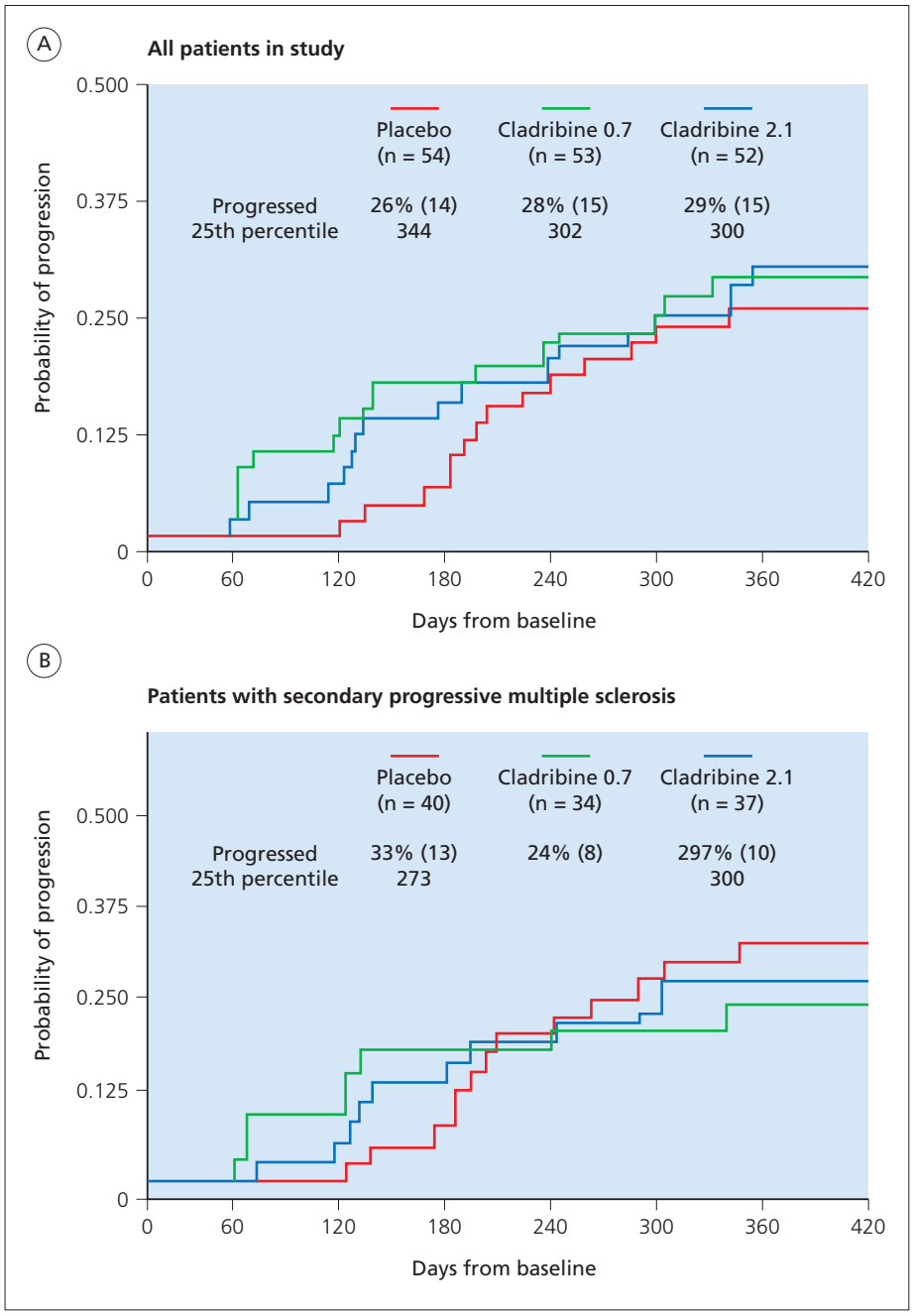


Figure 18.9 Treatment of multiple sclerosis with cladribine. Probability of disease progression (A) All patients; (B) Secondary progressive multiple sclerosis. This study was underpowered and of insufficient duration to determine whether cladribine would benefit patients with secondary progressive multiple sclerosis. Adapted from Rice *et al* (2000). © 2000, reproduced with permission of Lippincott Williams & Wilkins.

there had not been an adequate, long-range, properly controlled study to establish the validity of this axiom.

In a recent report, Zivadinov *et al* (2001a) randomized 88 ambulatory (baseline EDSS ≤ 5.5) patients with relapsing–remitting multiple sclerosis to receive either corticosteroids as needed to treat acute relapses, or on a predetermined schedule (every 4 months for 3 years and then every 6 months for 2 years). The regimen used methylprednisolone 1000 mg by intravenous infusion for 5 days followed by 4 days of oral prednisone (2 days each of 50 and 25 mg). To be eligible, patients needed to be at least 3 months removed from prior corticosteroid treatment and on no immune-modulating agents. Only the radiologist was blinded to study assignment. The results of this study were impressive. Only seven patients were lost to follow-up. The primary (MRI) and secondary (disease progression as measured by EDSS) outcomes favoured the scheduled regimen. Patients randomized to regular courses of corticosteroids showed a benefit in terms of T_1 lesion volume and brain parenchymal volume. Although no significant differences were seen in T_2 volume, surprisingly there was a trend suggesting that T_2 volume increased more in the group receiving scheduled corticosteroids. Clinical measures also favoured the scheduled regimen. These included confirmed EDSS change (≥ 1.0 worsening for baseline EDSS ≤ 5.0; ≥ 0.5 points for EDSS ≥ 5.5 at baseline; and changes confirmed for at least 8 months in the first 2 years and at least 12 months in years four and five), proportion with EDSS worsening, proportion converting to secondary progressive multiple sclerosis, and mean EDSS change. There were no

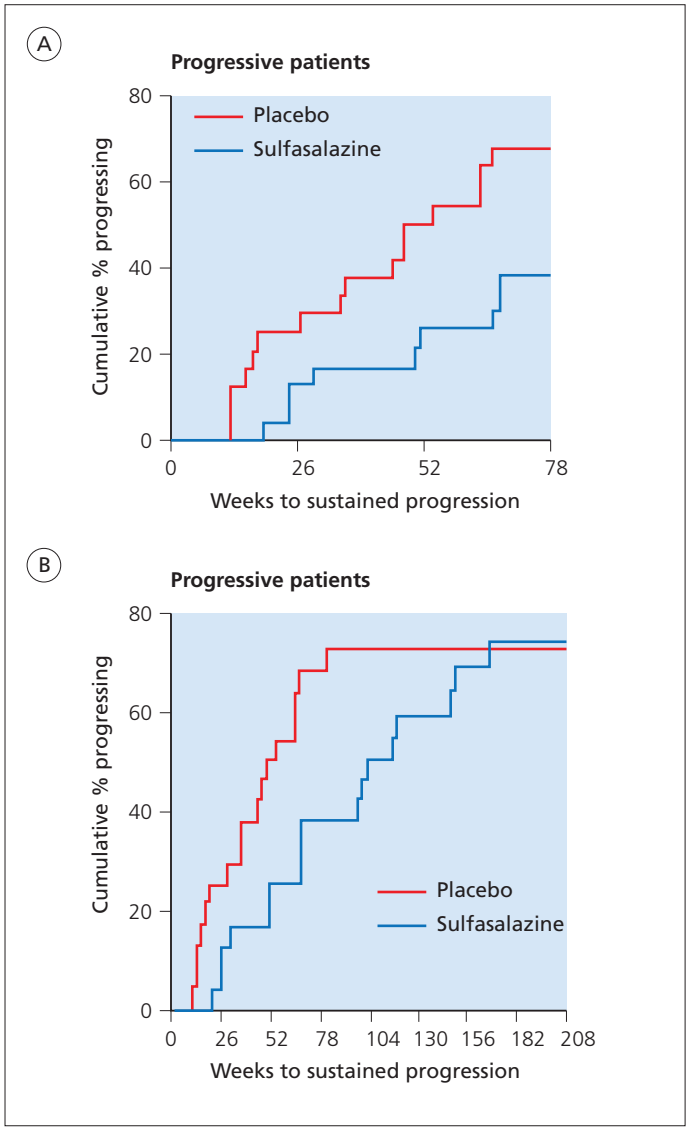


Figure 18.10 Treatment of active multiple sclerosis with sulfasalazine. (A) At the time of the interim analysis, there appeared to be an early treatment advantage for patients with progressive MS. (B) This later disappeared with prolonged follow-up. The data monitoring committee wisely did not terminate the trial early 'for apparent efficacy'. Adapted from Noseworthy *et al* (1998). © 1998, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

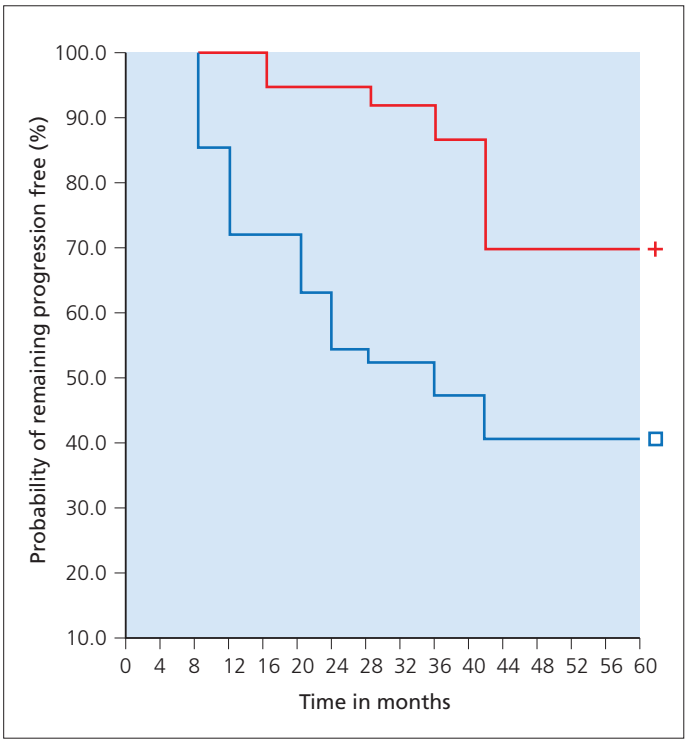


Figure 18.11 Treatment of relapsing–remitting multiple sclerosis with scheduled pulses of methylprednisolone (MP). Time survival curve to the onset of sustained EDSS score worsening. Log rank test $p < 0.001$. + = pulse MP; □ = control group. Adapted from Zivadinov *et al* (2001a). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

differences in relapse rates, number, or time to relapse (Figure 18.11). Are these findings definitive? Regrettably not. Although certainly they are of great interest in that this is the longest trial to date (5 years) and corticosteroids are inexpensive and generally well tolerated; the putative effects on cerebral atrophy reported are, to date, unmatched so that the study needs to be repeated. The decision not to blind the evaluator was a major design flaw. This omission may have significantly biased the clinical assessments, lending a spurious credence to the reported result (Noseworthy *et al* 1994). That said, the MRI evaluations were blinded and seem robust, although cerebral atrophy measures have not been validated as definitive outcomes. Cerebral volumetric measures are clearly influenced in the short term by the use of corticosteroids, and artefacts arising from suppression of inflammation. If independently confirmed, the findings would suggest that regularly administered corticosteroids delay or prevent irreversible tissue injury. In turn, such a result would support the hypothesis that corticosteroids act to inhibit nitric oxide and excitotoxic mechanisms of neuronal and axon injury (see Chapter 10). We are not aware that a confirmatory trial is under way.

As we discuss in Chapter 4, new episodes cluster in women with relapsing–remitting multiple sclerosis during the puerperium. For this reason, De Séze *et al* (2004) treated 20 women who had recently completed a pregnancy prophylactically with methylprednisolone (1 g monthly for 6 months) and noted a lower relapse rate (0.8 ± 0.41) compared with 22 females observed expectantly a few years earlier (2 ± 0.66).

THE BETA INTERFERONS

The 1990s were dominated by the publication of large clinical trials evaluating the three brands of IFN-β and glatiramer acetate as disease-modifying drugs in multiple sclerosis, and the consequent managed introduction of these products into clinical practice. Interferons were first used in multiple sclerosis because of their antiviral activities. At first, no emphasis was placed on the type of interferon and each was assessed after administration by the systemic or intrathecal route. A series of pilot studies, mostly uncontrolled and involving small numbers of patients, was performed in the 1980s. These involved IFN-α (Camenga *et al* 1986; Knobler *et al* 1984), IFN-β given systemically

(Baumhefner *et al* 1987; M. Huber *et al* 1988; K.P. Johnson *et al* 1990; Ververken *et al* 1979) or by the intrathecal route (Confavreux *et al* 1986; Jacobs *et al* 1981; 1982; Milanese *et al* 1990), and IFN-β (Panitch *et al* 1987a; 1987b). The role of IFN-α and IFN-γ is discussed above. In general, many details of these inaugural studies are now more of historical interest than providing evidence for the clinician wishing to assess the role of IFN-β in the management of multiple sclerosis, since they have been updated and superseded by the pivotal clinical trials discussed below. However, the pioneering work of Larry Jacobs (1938–2001) should be mentioned.

Initially, Jacobs carried out an unblinded trial of intrathecal natural IFN-β in 20 patients (Jacobs *et al* 1981). There was an effect on relapse rate and this work was extended to a single-blind (sham lumbar puncture) study in which 69 patients also showed a reduction in annual relapse rate (0.8 in treated patients compared to 1.5 in controls; $p < 0.001$: Jacobs *et al* 1986b; 1987). There were practical problems associated with the use of intrathecal interferon and difficulties in obtaining natural IFN-β. Together with results suggesting an increase in disease activity in patients receiving natural interferon (Milanese *et al* 1990), no further progress was made until recombinant IFN-β was shown to be effective after parenteral administration. It was subsequently recognized that the immunological effects and physiological situations that characterize release of the naturally occurring interferons differ for IFN-α and IFN-β from IFN-γ. The results of clinical trials led to the conclusion that IFN-γ is contraindicated in multiple sclerosis and that IFN-α is not obviously effective, although its use has not altogether been abandoned (see above). However, IFN-β survived this filtration process, attracting increasing attention because of the accumulation of evidence for its partial efficacy together with vigorous marketing on a scale to which neurologists looking after people with multiple sclerosis had not previously been exposed. By comparison with azathioprine, for example, the processing of comparative clinical results attributable to IFN-β (see below) has been demonstrably less restrained.

In summary, the IFNB Multiple Sclerosis Study Group trial showed that patients receiving IFN-β1b (Betaseron 8 MIU by self-administered subcutaneous injection on alternate days) had a reduced relapse rate, although the effects on disability and disease progression did not reach conventional levels of statistical significance. Much was made of the reduction in MRI activity seen in the IFN-β1b (Betaseron) study and the extent to which this provided evidence for a disease-modifying effect. Subsequently, IFN-β1a (Avonex; 6 MIU intramuscularly on a weekly basis) was shown to reduce relapse rate and slow the rate of disability and the time to progression. The report on IFN-β1b (Betaseron) appeared in 1993, with an update in 1995. The study of IFN-β1a (Avonex) received much advance publicity but did not appear until January 1996. Sandwiched between these primary publications was a deluge of commentaries, vigorous marketing efforts by the pharmaceutical companies who stood to gain from the introduction of these products, and the jottings of several seriously ill-informed journalists. The immediate consequence was that, initially, neurologists were asked to prescribe IFN-β before it was licensed or widely available and often in settings where governments restricted its use. This complex situation subsequently evolved. Interferons became widely available for use in relapsing–remitting multiple sclerosis and, in some countries, for secondary progressive disease. Governmental efforts to ration their use still vary widely. Many countries and groups of opinion leaders have developed guidelines for prescribing these agents. Despite these efforts, however, there remains no evidence-based definition of 'responder' status or 'treatment failure'. Consequently, practitioners and patients struggle daily with decisions of when to start, change or stop the use of these agents.

The mechanisms of action

Most cells express receptors for type 1 interferons. IFN-α and IFN-β share and compete for the same site, transducing signals through protein tyrosine kinases, phosphorylation of signal transducers and activation of transcription factors (STAT1 and STAT2), formation of the IFN-stimulated gene factor 3 from the association of STAT1 and STAT2 with the p48 protein, and binding of this gene factor to promoter elements resulting in gene transcription (Karpusas 1998). IFN-γ uses a different receptor but stimulates some of the same intracellular signalling molecules. Collectively, the interferons show a variety of antiviral, antimicrobial, antitumour and immunological effects (for review, see Goodkin 1994; Weinstock-Guttman *et al* 1995; Yong 2002). If IFN-β has a role in modifying the long-term course of multiple sclerosis, it is almost certainly not through any effect on the response to viral infection, as originally suggested, and the recent logic for continued use in clinical practice rests on the results of laboratory studies that shift the emphasis on mode of action to immunological properties. T-cell-derived IFN-γ has mainly proinflammatory effects and this explains why it increases disease activity in multiple sclerosis.

The logic for using IFN-β is now based not only on the argument that IFN-β inhibits the actions of IFN-γ, but also from a wide variety of additional presumed mechanisms of action including inhibition of T-cell activation, modulation of cytokine production and reduction in T-cell migration. In this respect, IFN-β can be considered as an anti-inflammatory cytokine but it also enhances some components of the immune response. This literature is abundant and often conflicting. Research remains active and, as expected given the plethora of potential sites of activity, the story is self-evidently incomplete and not without its share of ambiguities on the specific immunological effects and their relevance for treated patients. Inevitably, individual commentators tend to focus on the mechanisms that address their preferred concepts for the pathogenesis of multiple sclerosis. We are not exempt from these accusations of parochialism. Table 18.2 provides contemporary references for recent work on the potential mechanisms of action of IFN-β, a subject comprehensively reviewed by J. Zhang *et al* (2002). Exposure of microglia to IFN-γ *in vitro* increases the expression of cell surface class II MHC antigen (Woodroofe *et al* 1989) and the constitutively expressed T helper type 1 (Th1) costimulatory molecule B7 (K.E. Williams *et al* 1994). This upregulation is inhibited by IFN-β in a dose-dependent manner. The effect is most pronounced when IFN-β is introduced *in vitro* prior to IFN-γ exposure but is still evident when IFN-β is added after exposure of microglia to IFN-γ. Since this inhibition is not associated with a decrease in class II mRNA within cells, the mechanism is considered to be post-transcriptional and, given that class II heavy chain accumulates within cells, presumably post-translational. Revel *et al* (1995) have shown that the molecular interactions of IFN-β and IFN-γ involve the STAT1 transcription

Table 18.2 Presumed mechanisms of action of the beta interferons

Inhibits T-cell costimulation and/or activiation processes

- Inhibits IFN-γ-induced expression of MHC class II molecules and other molecules required for T-cell activation (Arnason *et al* 1996)
- Modulates costimulatory molecules on dendritic and other cell types (Y.M. Huang *et al* 2001a; 2001b; 2001c; 2001d; Z. Liu *et al* 2001)
- Reduces precursor frequency of myelin-reactive T cells (Kozovska *et al* 1999; Zang *et al* 2000b)
- Treatment-induced reduction in costimulatory molecules (Shapiro *et al* 2003)
- Treatment-induced reduction in the number of antigen-presenting dendritic cells (Bergh *et al* 2004)

Modulates anti-inflammatory and proinflammatory cytokines

- Increases IL-10 and IL-4 production/expression at protein and mRNA levels (Ozenci *et al* 2000; Rep *et al* 1996; Rudick *et al* 1996b; 1998b; Tuohy *et al* 2000)
- Decreases IL-12 production (Karp *et al* 2001; McRae *et al* 1998; Tuohy *et al* 2000)
- Decreases TNF-α and IFN-γ production (Kozovska *et al* 1999; Rep *et al* 1996; Zang *et al* 2000b)
- Suppresses Th1 cells and upregulates IL-10 production (Zang *et al* 2003)

Decreases aberrant T-cell migration

- Enhanced shedding of VCAM-1 from endothelium into soluble form (Calabresi *et al* 1997c)
- Decreases T-cell migration (Prat *et al* 1999)
- Reduced integrin gene expression (Muraro *et al* 2004)
- Inhibits expression of mRNA for MIP-1α, RANTES, and CCR5 (Zang *et al* 2000a; 2001)
- Reduces migration of T cells toward the chemokines RANTES and MIP-1 (Zang *et al* 2001)
- Decreases IL-2-stimulated secretion of MMP (Leppert *et al* 1996; Lou *et al* 1999)
- Treatment-induced reduced MMP-9 levels in PPMS (Yushchenko *et al* 2003)
- Treatment-induced enhanced TIMP-1 levels in RRMS (Karabudak *et al* 2004)
- Reduces secretion of TNF-α and IL-1 (Lou *et al* 1999)

MHC = major histocompatibility complex; IL = interleukin; mRNA = messenger ribonucleic acid; TNF = tumour necrosis factor; VCAM = vascular cell adhesion molecules; MIP = macrophage inflammatory proteins; RANTES = regulated on activation, normal T-cell expressed and secreted; CCR = chemokine receptor; MMP = matrix metalloproteinases; TIMP-1 = natural tissue inhibitors of MMPs. Adapted from Zhang et al *(2002) with permission.*

factor and they propose a model involving antagonistic and synergistic actions on different genes whose products relate to cell activation. The increased class II antigen expression on microglia enables these to function as antigen-presenting cells and the proliferation of primed T cells exposed to antigen and IFN-γ activated microglia is inhibited by IFN-β (G. Hall *et al* 1997a). It is well recognized that IFN-β has an antiproliferative effect on T (and other non-immune) cells, inhibiting markers of activation such as IL-2 receptor, transferrin receptor and CD2 (A. Noronha *et al* 1993). Others have shown that the release *in vitro* of IFN-γ by mononuclear cells is reduced in patients treated with IFN-β (Petereit *et al* 1997).

Antigen-specific and IL-2-stimulated proliferation of Th1 cells are inhibited by IFN-β but without reducing their secretion of IFN-γ, TNF-α or macrophage inflammatory protein-1α. In fact, IFN-γ secretion is slightly increased, further demonstrating that the effects of IFN-β are complex and cannot simply be seen as suppression of IFN-γ-stimulated proinflammatory events (M. Pette *et al* 1997). In a comprehensive assessment, H. Jiang *et al* (1995) showed that IFN-β inhibits the ability of human antigen-presenting cells and B lymphocytes to induce T-cell proliferation. These inhibitions are associated with reduced expression of class II MHC antigens and adhesion molecules.

Taken together, these *in vitro* results suggest that IFN-β prevents the arrival of T cells and limits antigen presentation within the central nervous system, disengaging the amplification of local immune responses involving microglia and (antigen-specific) infiltrating T cells. IFN-γ also promotes the cytotoxic and phagocytic activities of microglia by increasing their respiratory burst and inducing the release of many mediators, but the interaction of IFN-γ and IFN-β on these properties is less straightforward. Rodent microglia exposed to IFN-γ increase the expression of Fc receptors and this effect is enhanced by IFN-β (G.C. Hall *et al* 1997b). IFN-β also directly stimulates the production of potentially harmful cytokines including TNF-α by microglia, further promoting their cytotoxic and phagocytic properties. TNF-α has a complementary effect on the ability of IFN-γ to increase class II antigen expression, demonstrating that intricate networks exist between pro- and anti-inflammatory cytokines. In samples obtained from patients before and during treatment, Brod *et al* (1996) showed that mitogen-induced production of cytokines (IFN-γ, IL-2, IL-6 and IL-10 but not IL-4 or TNF-α) is increased by IFN-β. Porrini *et al* (1995) took a slightly different position claiming that, *in vitro*, IFN-β induces the production of IL-10 and cytokines characterizing Th2 cells – a response not reproduced by IFN-γ. IL-10 released in response to IFN-β inhibits the production of TNF-α and IL-6 induced by IFN-γ and other macrophage activators. Others have since confirmed the antiproliferative effect of IFN-γ on human T cells *in vitro*, adding the observation that cooperation between T and B cells is also inhibited and emphasizing the anti-inflammatory consequences of the associated enhanced IL-10 production (Rep *et al* 1996; Rudick *et al* 1996b; see Chapter 11). IL-1 and IL-10 and transforming growth factor-β (TGF-β) tend to reduce class I antigen expression, providing evidence for a cascade of anti-inflammatory effects on antigen presentation in the central nervous system (Cowan *et al* 1991b; Racke *et al* 1991). IFN-β also inhibits antigen presentation of peripheral blood mononuclear cells through an effect on class II antigen expression (H. Jiang *et al* 1995). IFN-β inhibits IL-1-induced and IFN-α-induced production of nitric oxide (L.L. Hua *et al* 1998) and protects neurons from nitric oxide-mediated damage to mitochondrial complexes II/III and IV (Stewart *et al* 1998).

IFN-β and IFN-γ may therefore independently enhance the cytotoxic and phagocytic properties of microglia. At the very least, there does not appear to be complete reciprocal inhibition. Conversely, the antigen-presenting effects of IFN-γ-stimulated microglia are inhibited by IFN-β (G. Hall *et al* 1997a; 1997b). Given the part inhibitory and part complementary effects, it would be too simple to designate IFN-γ and IFN-β as entirely proinflammatory and anti-inflammatory cytokines, respectively.

The fact that IFN-β also inhibits class II expression on endothelial cells [in this situation, probably through a transcriptional mechanism (A. Miller *et al* 1996)] provides an additional potential mechanism of action through effects on cell migration across the blood–brain barrier (Huynh *et al* 1995). Further evidence is

provided by the demonstration that the IL-2-induced secretion of metalloproteinases by T cells, which normally enhances their ability to adhere and migrate through endothelial barriers, is reduced by preincubation *in vitro* with IFN-β, probably by a direct effect on IL-2 receptors (Leppert *et al* 1996). Others have assessed changes in the endothelium and conclude that IFN-β, by reducing the secretion of matrix metalloproteinases, inhibits cell migration and limits the ability of T cells and natural killer cells to cleave fibronectin on the basement membrane of endothelial cells (Stuve *et al* 1996). These studies specifically implicate matrix metalloproteinase-9. Corsini *et al* (1997) showed a reduction in adherence between mononuclear cells from patients treated for at least 6 months with IFN-β on cultured brain endothelia derived from a patient with multiple sclerosis. This was associated with reduced expression of HLA-DR on endothelial but not mononuclear cells, and with no effect on other adhesion molecules. Related work shows also that IFN-β affects the migratory activity of mononuclear cells by inhibiting their production of matrix metalloproteinase-9 (Stuve *et al* 1997). Recently, two groups have studied the effects of interferons on matrix metalloproteinase-9 and a tissue inhibitor of metalloproteinase (TIMP-1). Yushchenko *et al* (2003) showed that treatment with IFN-β1b produced reduced levels of serum matrix metalloproteinase-9 in all but one of 19 patients with primary progressive multiple sclerosis; there were no consistent changes in TIMP-1 levels. Karabudak *et al* (2004) reported that IFN-β1a treatment induced transient increases in TIMP-1 levels compared with baseline (at 3 and 6 months but not at 1 year) in a study of 16 patients with relapsing–remitting multiple sclerosis. However, no consistent changes were detected in matrix metalloproteinase-9 levels. Again, the relevance of these findings remains uncertain.

In a study of 35 patients with relapsing–remitting multiple sclerosis and 12 with secondary progressive disease, Shapiro *et al* (2003) demonstrated that treatment with IFN-β1a (Rebif) may induce changes in the ratio of costimulatory molecules (for example, suppression of CD80 and induction of CD86) detected within the first year of treatment that favour a Th2 predominance. They raise the theoretical concern that these patients could be at risk of humoral mediated autoimmunity or allergic phenomena.

An effect of IFN-β on lymphocyte migration, and hence inflammation, is also provided by the demonstration of reduced very late antigen-4 (VLA-4) expression on monocytes (Soilu-Hanninen *et al* 1995) and lymphocytes from a small group of treated patients, but this finding could not be reproduced *in vitro* (Calabresi *et al* 1997a; Muraro *et al* 2000). The interferons may increase shedding of vascular cell adhesion molecule (VCAM) and intracellular adhesion molecule-1 (ICAM-1) from endothelial cells thereby increasing circulating levels of these adhesion molecules (Calabresi *et al* 1997c). IFN-β treatment could thereby block migration of activated T cells by reducing the concentration of endothelial membrane-bound adhesion molecules. Alternatively, once shed from the cell surface, these soluble adhesion molecules may block their respective receptors on activated peripheral blood mononuclear cells [for example, soluble ICAM-1 binding to lymphocyte function associated antigen (LFA) and Mac-1; and soluble VCAM binding to VLA-1]. In a recent study of 50 patients with relapsing–remitting multiple sclerosis treated with IFN-β1a and IFN-β1b, Muraro *et al* (2004) reported that integrin gene expression of VLA-4 and LFA-1 is reduced in patients classified as 'IFN responders', raising the intriguing (but unconfirmed) suggestion that transcription of integrin genes may correlate with the treatment effect.

In summary, IFN-β probably exerts its effects through a variety of mechanisms. These include actions that reduce T-cell and monocyte activation and lymphocyte proliferation, decrease the proinflammatory cytokine bias that is thought to underlie some of the steps in tissue injury, reduce the IFN-γ upregulation of class II expression, diminish antigen presentation, and reduce T-cell migration through the blood–brain barrier. As discussed later, the putative mechanisms of action of glatiramer acetate differ from those for the interferons but with some interesting overlap and redundancy. These major differences raise a possible role for combination therapy.

The pivotal trials

The evidence that informed prescribing patterns, and led to product licences for the three brands of IFN-β, was derived from a series of pivotal studies incorporating randomized, double-blind and placebo-controlled designs carried out in the 1990s. IFN-β1b is produced by recombinant DNA technology using *Escherichia coli*. It differs from natural human and recombinant IFN-β1a (made in Chinese hamster ovary cells) in having 165 amino acids (lacking the methionine at position 1), a serine residue substituted for cysteine at position 17 to prevent incorrect disulphide bond formation, and no glycosylation of the asparagine residue at position 80. In the pivotal trials IFN-β1a (Avonex) was administered by weekly intramuscular injection (6 MIU), and IFN-β1a (Rebif; 22 or 44 μg thrice weekly) and IFN-β1b (Betaferon; 8 MIU), and as alternate day subcutaneous injections. These regimens were justified by the demonstration that serum levels of IFN-β1b peak between 8 and 24 hours and return to baseline by 48 hours (O.A. Khan *et al* 1996). There are no obvious differences between IFN-β1b and IFN-β1a in their biological activity or *in vivo* pharmacokinetics. Each is associated with the development of neutralizing antibodies. Here, we review the efficacies and adverse effects of these therapies, and the position that has emerged on the timing of treatment with respect to disease course. In turn, these inform the evidence base for the role of IFN-β in the management of multiple sclerosis at several stages of the illness. The sponsors of trials n multiple sclerosis have used an inconsistent and unhelpful format for designating doses of the interferons. To avoid controversy with regard to bio-equivalence, we refer to these studies using the doses as published. For reference, subcutaneous IFN-β1b has been tested in doses of 1.6 and 8 MIU (Betaseron) and 22 and 44 μg (Rebif). Intramuscular IFN-β1a (Avonex) has been tested predominately at 30 μg. On a mass basis, 6 MIU equates to 22 μg and 8 MIU to 44 μg.

IFN-β1b (Betaferon)

The pilot study of IFN-β1b was used to determine primary outcome measures for the definitive trial (K.P. Johnson *et al* 1990). Compared with seven controls, treatment in 24 patients using different doses of IFN-β1b showed a modest effect on relapse frequency. During treatment, patients receiving IFN-β1b had a

relapse rate of 0.7 per year compared with 0.9 per year in the placebo group; and the probability of remaining relapse free at 3 years was 83% compared with an estimated pretreatment rate of 63%. There was no effect on disability. In fact, the treated group did marginally worse.

The phase three trial was conducted simultaneously in Canada and the United States (IFNB Multiple Sclerosis Study Group 1993). It involved 372 patients, each having two relapses in the previous 2 years and with pre-entry EDSS scores <5.5 (the mean was about 3.0; Table 18.3). Treated cases were younger and had slightly longer disease duration. Corticosteroids were used during the trial period by 35% and 50% of treated and placebo cases, respectively. Those who did not complete the study (19%) were considered to have remained stable from the point at which they dropped out. The study was not therefore analysed strictly on an intention to treat basis. The results were broadly similar in the Canadian and United States groups. Most commentators consider this to have been a single trial, although attempts were made to represent these as independent and hence confirmatory studies, respectively.

In patients receiving 8 MIU of IFN-β1b, both primary outcome measures – relapse rate and number of relapse-free patients – achieved statistically significant results ($p = 0.0001$ and $p = 0.007$, respectively). Of the secondary end points, reduction in relapse rate in those who continued to relapse ($p = 0.001$), increase in time to first relapse ($p = 0.015$) and second relapse ($p = 0.007$), and reduction in the proportion of relapses judged to be moderate or severe (placebo vs. 8 MIU, $p = 0.002$) were also achieved.

The subsequent experience of these participants was later reported. The overall tone of the second publication (IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group 1995) was notably more sober than the initial paper. Participants had remained in the study for a median time of just under 4 years. Taking this entire period, the reduction in relapse rate associated with the use of IFN-β1b reported in 1993 was maintained at follow-up (8 MIU: 0.78 per year compared with 1.12 for the placebo group; $p = 0.0006$). The main effect of treatment was achieved in the first year. Although there was a reduction in relapse rate, both in treated patients and the placebo group, in each subsequent year, the cumulative reduction beyond year 1 was in fact greater as part of the untreated natural history (–0.63 between years 2 and 5 in placebo-treated patients compared with –0.39 in the treated group; Table 18.3 and Figure 18.12). However, this observation may be somewhat disingenuous since the baseline was lower at the start of year 1 in the treated group, therefore providing less room for manoeuvre in terms of further reduction in relapse rate by comparison with controls. Understandably, the authors emphasized these results as showing a continuing difference in exacerbation rates between treated and placebo groups, year on year, borrowing the substantial reduction in the first year for the subsequent cumulative reduction in

Table 18.3 **IFN-β1b: updated report of pivotal trials**

	Placebo	1.5 MIU	8 MIU
Exacerbation rates			
Enrolled	123	125	124
Number entering year 5	56	52	58
Overall exacerbation rate (baseline-year 5)	1.12[a] (1.02–1.23)	0.96 (0.87–1.06)	0.78[a] (0.70–0.88)
Year-on-year exacerbation rates			
Year 1	1.44	1.22	0.96
Year 2	1.18	1.04	0.85
Year 3	0.92	0.80	0.66
Year 4	0.88	0.68	0.67
Year 5	0.81	0.66	0.57
Reduction in exacerbation rate			
Baseline-year 1	–0.36	–0.48	–0.74
Year 2–5	–0.63	–0.56	–0.39
Disability			
Enrolled	123	125	124
Number entering year 5	56	52	58
No. with EDSS >1 point	56/122 (46%)	59/125 (47%)	43/122 (35%)[b]
Baseline EDSS <3	26/58 (45%)	30/59 (51%)	20/55 (36%)
Baseline EDSS >3	30/64 (47%)	29/66 (44%)	23/67 (34%)
Median time to progression (years)	4.18	3.49	4.79[c]
MRI: lesion load			
Enrolled	73	66	78
Number entering year 5	72	61	75
Baseline MRI (median)	1503	1086	1525
Completing year 1	+6.7	+5.7	–4.9
Completing year 4	+30.2[d]	+10.6	+3.6[d]
Increase: year 2–5	+23.5	+4.9	+8.7

a $p = 0.0001$; b $p = 0.096$; c $p = 0.087$; d $p = 0.04$.

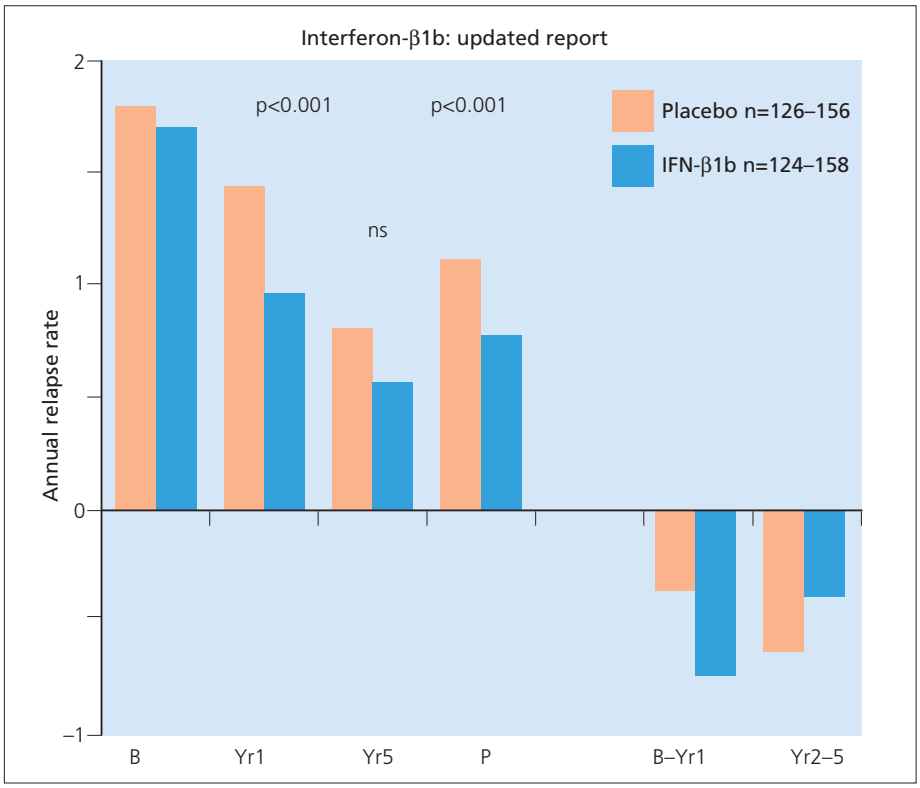


Figure 18.12 Annual relapse rates at baseline (B), baseline to year 1 (Yr1) and baseline to year 5 (Yr5) and in placebo-treated patients (P) in a trial of IFN-β1b; the rate of reduction is shown from baseline to end of year 1 (B-Yr1) and end of year 1 to end of year 5 (Yr2-5). Adapted from the IFNB Multiple Sclerosis Study Group (1993; 1995). © 1993, 1995, reproduced with permission of Lippincott Williams & Wilkins (lww. com).

relapse rate over the entire period. In this second report, once again IFN-β1b at a dose of 8 MIU reduced the proportion of patients judged to have a moderate or severe relapse compared with placebo ($p = 0.012$) although the data are not shown.

It has since been much debated whether a modest effect on relapse rate is useful for the majority of patients with multiple sclerosis. Relapses are distressing but usually self limiting, although they cause disability if recovery is poor. IFN-β1b may reduce relapse severity but the magnitude of this putative protection is somewhat unclear. In the IFN-β1b trial reports, 'moderate and severe' relapses are grouped together. The numbers of patients with each type of relapse, including those of 'unknown' severity, are not given. That said, it may be that, in protecting individuals from about one relapse every 3 years, IFN-β1b may be more likely to reduce a severe attack than a mild one. Relapses affecting the pyramidal and cerebellar systems are often relatively disabling, at least in the short term, and there were fewer of these in the treated patients. The effect on relapse rate reduced the need for hospitalization, and presumably also the impact on aspects of daily living, although this could not directly be assessed. Critics pointed out that the relapses were self reported and not universally confirmed by the attending neurologist. We understand that analysis only of those relapses that were physician confirmed was still highly significant and so take a charitable view on this design fault, accepting that there was no bias in the distribution of pseudo- and non-relapses in treated patients compared with the placebo group.

In many natural history studies, relapse frequency has not emerged as a factor which predicts disability. In recent studies from the Mayo Clinic (with a small cohort of patients followed closely for several decades), it has been difficult to confirm a close link between relapses and disability. No single demographic or disease variable (including relapse number in the first year) closely predicted prognosis (Pittock *et al* 2004a). In this series, as reported previously (Confavreux *et al* 2000), relapses did not influence further progression after reaching EDSS 3.0 (Pittock *et al* 2004b). In the large Canadian series, however, the number of relapses in the first 2 years, and time to the first relapse after presentation, did each correlate with eventual disability (Weinshenker *et al* 1991a; see also Chapter 4). This has encouraged people with multiple sclerosis that the reduction in relapse rate may have a dividend for an altered natural history of disease. It remains completely unknown, however, whether a reduction in relapse rate attributable to treatment (if this was shown to be long lasting by appropriately designed trials) shares the same good prognosis enjoyed by untreated patients experiencing a relatively relapse-free existence as part of their natural history.

Much has been made of the extent to which the MRI results influenced the overall impact of the IFN-β1b study. The IFNB Multiple Sclerosis Study Group studied a cohort of cases with serial assessments of lesion load (an indicator of the volume of affected brain), supplemented by measures of new and active lesions (Paty *et al* 1993). Comparable at entry, IFN-β1b-treated cases showed a reduction in lesion load within the first year (–4.9%) compared with the placebo group (+6.7%). These differences were maintained into the year 5 but, here too, the early effect attributed to IFN-β1b slipped marginally with time (Figure 18.13). Thus, both for the effect on relapse frequency and MRI lesion load, the experience of the first year proved crucial in this pivotal trial (Table 18.3).

In a subsequent study involving patients not recruited for the IFN-β1b (Betaseron) trial, L.A. Stone *et al* (1995) compared the contrast enhancing new lesion rate in the 7 months before and 6 months after introduction of IFN-β1b. A minimum pre-treatment rate of 0.5 lesions/month was required for entry and

13 of the 14 participants showed a reduction in active lesions. This represented an average change from 3.1/month to 0.5/month ($p = 0.002$). The number was 230 before and 20 after starting treatment with IFN-β1b, a reduction of 90%. Many patients had been studied over a longer period (up to 50 months) and the new lesion rate changed from 2.7/month to 0.2/month. These patients had eight clinical episodes in the pre-treatment period and four during treatment – a surprisingly high number given the MRI results. As an extension of this work, L.A. Stone *et al* (1997) prospectively studied 29 patients having >0.5 lesions/month during a 7 month qualification period. Eighty-six per cent of scans were active before and 33% were active during treatment with IFN-β1b. The median number of new lesions per patient per month dropped from 2.5 to 0.17 ($p < 0.0001$). Inevitably, there was variation between patients, prompting the authors to define a group of nonresponders but these did not have identifiable clinical or natural history characteristics.

A different marker of biological efficacy, measurement of urinary myelin basic protein-like material, was used for some participants in the IFN-β1b study (Whitaker *et al* 1995b). In so far as levels of this breakdown product represent a marker of disease progression and both number of lesions and total MRI lesion load, this result provided further surrogate evidence for efficacy. However, randomization bias prevented detailed analysis of the effect of IFN-β on urinary myelin basic protein.

There was no statistically significant effect of IFN-β1b on disability in these mildly affected patients participating in the North American study and that situation did not change with extension to 5 years (Figure 18.14). Thus, 43 of 122 (35%) treated patients showed a sustained (>6 months) deterioration of ≥ 1 EDSS points compared with 59 of 122 (46%) of the placebo group ($p = 0.10$). These results were uninfluenced by stratification for disability (baseline EDSS <3 and ≥ 3 at entry). It has been argued that restriction of the trial to include only stable, ambulant, relapsing–remitting patients did not give the study adequate power to assess this outcome. Thus, the results can be read as providing evidence for no effect on disability, or no evidence for an effect on disability. This difference in outcome may relate to the relative ease with which new episodes can be defined and the low stringency conditions used to assign relapses in this study, together with the insensitivity of scales routinely used to define disability. We have made the point repeatedly that inflammation and degeneration make different contributions to the pathological processes underlying relapse and progression. Saida *et al* (2005) randomized 205 patients from Japan with relapsing–remitting multiple sclerosis either to receive high- [250 μg (8 MIU)] or low-dose [50 μg (1.6 MIU)] IFN-β1b (Betaseron) three times weekly. As reported previously in the original North American trial, high doses of IFN-β1b were superior to low doses in reducing relapse rates and other measures of

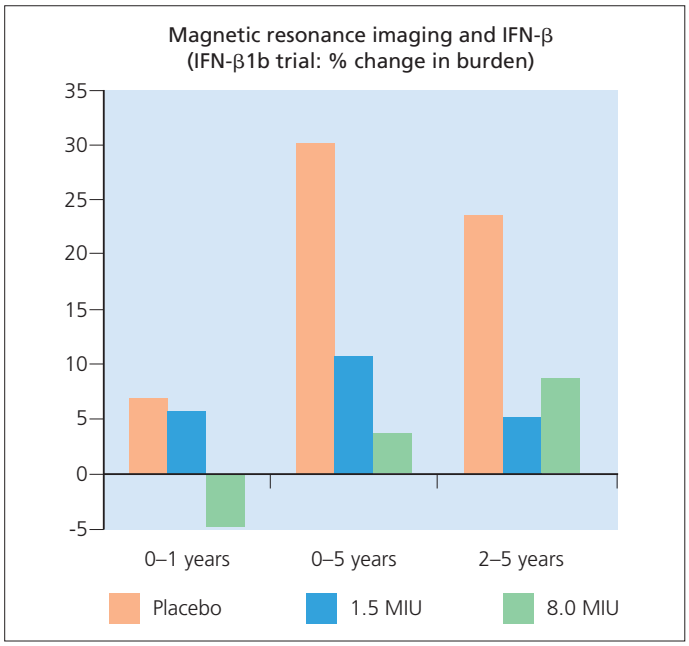


Figure 18.13 Annual change in MRI disease burden at baseline, baseline to year 1 and baseline to year 5 in patients receiving IFN-β1b; the rate of reduction is shown from baseline to end of year 1 and end of year 1 to end of year 5. Adapted from Paty *et al* (1993) and the IFNB Multiple Sclerosis Study Group (1993; 1995). © 1993; 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

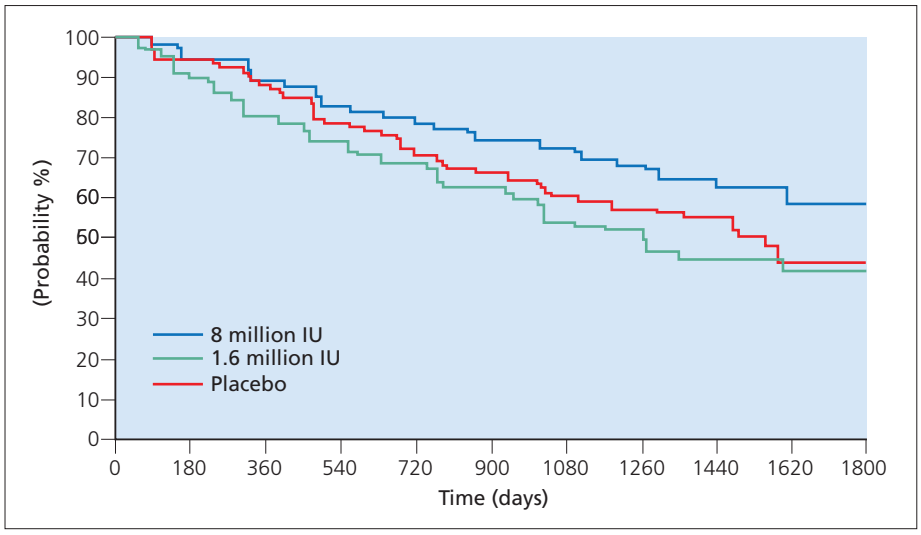


Figure 18.14: Kaplan–Meier curves showing, by treatment arm, the probability of avoiding progression of multiple sclerosis equal to at least 1 EDSS point. Adapted from the IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group (1995). © 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

disease activity. This suggests that, despite some differences in phenotype, IFN-β may be no less effective in Japanese populations than elsewhere.

IFN-β1a (Avonex)

The results of a study using IFN-β1a, with disability as the primary outcome measure, were first presented to a joint meeting of the American Neurological Association and Association of British Neurologists in October 1994 and immediately published in abstract form (Anon 1994). Despite widespread distribution of fly-sheets further advertising these results at scientific meetings and a description of the methodology (Jacobs *et al* 1995), no peer-reviewed publication of the results appeared until early 1996 (Jacobs *et al* 1996) by which time the procedure for granting a product licence in the United States and Europe was well advanced. In the trial, existing symptomatic treatments were not discontinued. Relapses were treated (at the discretion of physicians) with corticosteroids and immediate adverse effects of IFN-β1a were prophylactically managed with acetaminophen. Three hundred and one patients with clinically definite multiple sclerosis in the relapsing phase (some with persistent symptoms and signs), and with EDSS scores ranging from 1 to 3.5, were treated with placebo (n = 143 at entry; n = 87 for 2 years) or IFN-β1a (n = 158 and n = 85, respectively; Table 18.4). Each had two or more physician-documented relapses in the preceding 3 years but none in the previous 2 months, and the pretreatment exacerbation rate was >0.67 per year. Compliance with the trial protocol was good, with >99% of assessments completed. There were 23 early exits from the study but assessments continued in these patients. Sample size calculations allowed for 25% of patients to discontinue treatment but remain available for analysis on an intention to treat basis and with 10% lost to follow-up. The drop-out rate was <3%. The decision was taken to restrict recruitment to 288 patients (in fact, 301 had already been enrolled) and to stop the study a year earlier than planned. In retrospect, this was unwise because it has been assumed (wrongly according to the manufacturer) that premature termination of the study was taken with reference to interim efficacy analyses. Whatever the reason, this decision left the study significantly underpowered.

Treatment with IFN-β1a was shown to be associated with a slower rate of disability (defined in advance as deterioration by ≥ 1 point on the EDSS for ≥ 6 months; Table 18.4). The decision to stop the trial early left only 172 (IFN-β1a, n = 85; placebo, n = 87) participants observed for the intended duration of the study. Two years after the start, 22% of 158 patients who had received IFN-β1a were classified as treatment failures compared with 35% of the 143 placebo cases. At this point, two patients had not completed 6 months on the study; 14 (seven in each arm) had been involved for <1 year; 67 (IFN-β1a, n = 32; placebo, n = 35) had been studied for <18 months; and 134 (IFN-β1a, n = 56; placebo, n = 73) had been involved for <2 years (Figure 18.15). The numbers of treatment failures in those who completed 2 years were 18 of 85 (21%) in the IFN-β1a-treated group and 29 of 87 (33%) in the placebo group, respectively. Using the probability of sustained progression in the first year as an outcome also revealed the modest effect on disability (22% and 16% during year one, and 12% and 11% during year two, for placebo and treated patients, respectively; p = 0.02: Figure 18.16). These proportions did not differ between those who completed a second year in the study and those who did not.

Table 18.4 IFN-β1a (Avonex): pivotal trial

	Placebo	IFN-β1a
Number enrolled	143	158
Number completing year 1	136	151
Number completing year 2	87	85
Change in disability		
Sustained progression at year 1	22%	13%
Sustained progression at year 2 (all patients)[1]	35%	22%
Sustained progression at year 1	22%	13%
Sustained progression at year 2 (patients completing 2 years on study)	33%	21%
Change in EDSS at 2 years: –<1 point	12%	19%
Change in EDSS at 2 years: +<1 point	37%	24%[a]
Change in relapse frequency		
Relapse frequency at 2 years: <2	56%	68%
Relapse frequency at 2 years: >2	44%	32%
Change in relapse rate: all cases	–0.38	–0.53[b]
Change in relapse rate: at 2 years	–0.30	–0.59[c]
MRI		
Change in T_2 lesion volume: year 1	–3%	–13%[a]
Change in T_2 lesion volume: year 2	–7%	–13%
Number of Gd+ lesions: baseline	>174	>196
Mean number of Gd+ lesions: baseline	2.32	3.17
Number of Gd+ lesions: year 1	>124	>85
Mean number of Gd+ lesions: year 1	1.59	1.04[a]
Number of Gd+ lesions: year 2	>78	>49
Mean number of Gd+ lesions: year 2	1.65	0.80[d]

a p = 0.02; b p = 0.04; c p = 0.0002; d p = 0.05.
Gd = gadolinium.

Relapse rate (each exacerbation had to last >48 hours and be confirmed by a neurologist) was a secondary outcome measure. Overall, the reduction amongst treated patients was 18%. Fewer treated patients in the cohort who completed 2 years (12 of 85, 14%) had three or more exacerbations during the study than controls (28 of 87, 32%; p = 0.03). In the group studied for 2 years, annual exacerbation rates reduced from 1.2 to 0.61 per year (–0.59) in patients receiving IFN-β1a compared with a reduction from 1.2 to 0.90 per year (–0.30) in the placebo group (a 31% difference; p = 0.002). The reduction in the annual exacerbation rate per patient per year suggested less benefit for all randomized patients (0.82 for placebo compared with 0.67 for treated patients; p = 0.04) than for the subset who completed 104 weeks of follow-up (0.90 for placebo compared with 0.61 for treated patients; p = 0.002; Figure 18.17). In marked contradistinction to the IFN-β1b study, the change in relapse rate was not apparent until the second year of the study. The proportions free from any relapse at 2 years in the IFN-β1a and placebo-treated groups were 38% and 26%, respectively (p = 0.03), and there was no significant difference in time to first relapse between the groups (36 and 47 weeks, respectively; p = 0.34; Table 18.4). Partly in response to critical comments on the IFN-β1a study, the investigators subsequently re-analysed their results using more stringent outcome measures (Rudick

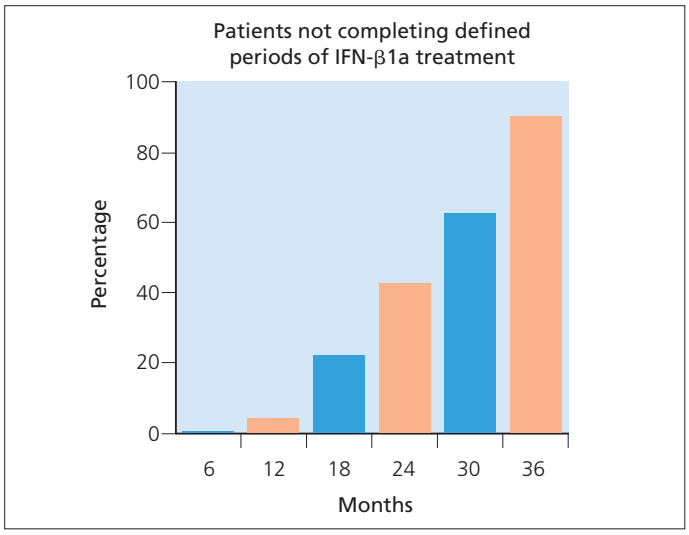


Figure 18.15 Percentage of patients not completing defined periods of treatment with IFN-β (Avonex). Data taken from Jacobs *et al* (1996). © 1996, reproduced with permission of John Wiley & Sons.

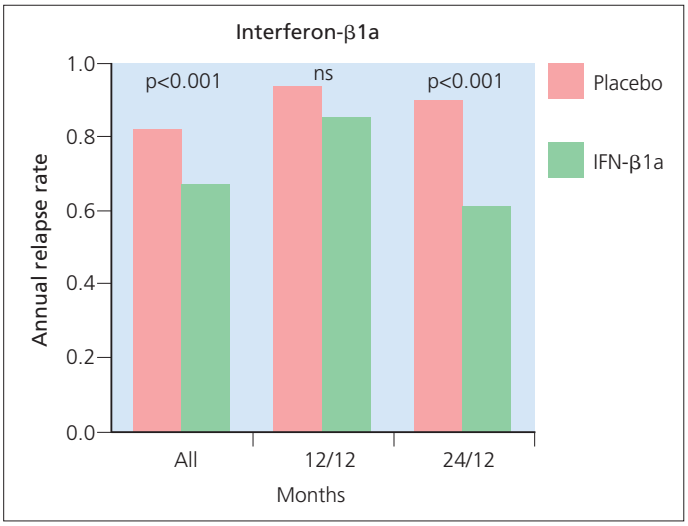


Figure 18.17 Annual relapse rates over the course of the study for all participants taking IFN-β1a (Avonex; All), and those completing year 1 (12/12) and year 2 (24/12). Adapted from Jacobs *et al* (1996). © 1996, reproduced with permission of John Wiley & Sons.

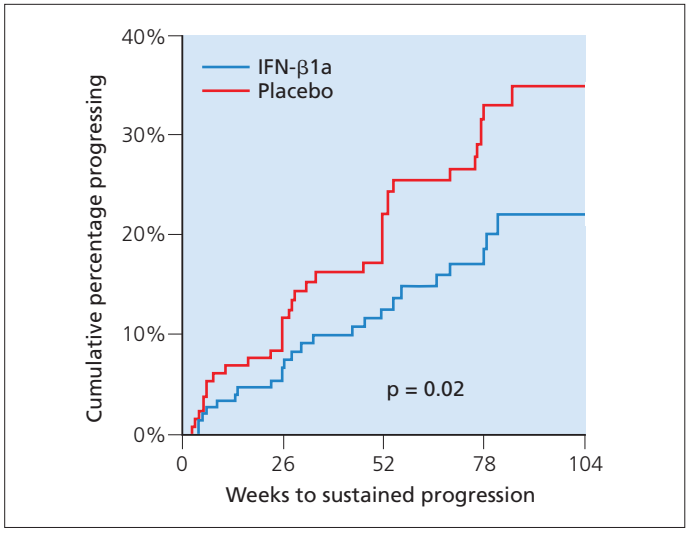


Figure 18.16 Kaplan–Meier failure time curve showing the cumulative percentage of patients taking IFN-β1a (Avonex) progressing according to number of weeks to beginning of sustained disability progression, compared with placebo-treated patients. Adapted from Jacobs *et al* (1996). © 1996, reproduced with permission of John Wiley & Sons.

et al 1997). Widening the gap between treated and placebo patients to >2 EDSS points or lengthening the duration of the >1 point difference to 1 year improved the benefits of IFN-β1a to 61% and 67% reductions, respectively, compared with the original estimate of 37% based on differences in the rates of accumulation of disability between groups. For those who did worsen, IFN-β1a failed to discriminate between functional systems. The authors concluded that IFN-β1a affects the magnitude but not the pattern of involvement in multiple sclerosis and that no factor other than randomization to the treatment arm could explain the outcome in this cohort of patients.

This trial also included surrogate markers of disease activity and lesion load. By year one, fewer IFN-β1a-treated patients had gadolinium enhancing lesions (30%) than in the placebo group (43%; p = 0.05) and there were also reductions in the number (p = 0.02) and volume (p = 0.02) of enhancing lesions. The assessment of T_2 lesion volumes, which featured strongly in the study of IFN-β1b, proved more difficult to resolve in the trial of IFN-β1a and the significant difference apparent at year one (–3% in IFN-β1a-treated patients compared with –13% in the placebo group; p = 0.02) was not maintained on completion of the second year (–7% and –13% respectively; p = 0.36; Table 18.4). The investigators subsequently updated these imaging results using a different method to measure T_2 lesion volume and reported a decrease in the number of new, enlarging, and new or enlarging T_2 lesions over 2 years. The increase in T_2 lesion volume was 628 mm^2 in patients receiving IFN-β1a compared with 1410 mm^2 in controls. In the subgroup with active lesions in advance of treatment, these differences were 1285 and 2980 mm^2, respectively, over the 2 years but with an increase in acquisition of new lesions in the treated group during the second year (J.H. Simon *et al* 1997). Pohl *et al* (2005) reported their experience treating 51 children and adolescents with relapsing–remitting multiple sclerosis using IFN-β1a once weekly. Although this was not a controlled trial, their report and the accompanying editorial (Banwell and Tremlett 2005) comparing pre- with post-treatment relapse rates suggested that children aged <16 years may benefit and tolerate IFN-β1a in this setting.

IFN-β1a (Rebif)

The effects of IFN-β1a (Rebif) were first assessed in 68 patients using MRI measures as outcome (Pozilli *et al* 1996). The average number of gadolinium-DTPA enhancing lesions decreased from three (SD 4.3) per month during the 6 months prior to treatment with 3 or 9 MIU subcutaneously three times weekly, to 1.3 (SD 2.2) lesions per month during the 6 months on treatment. The

OWIMS study (Once Weekly Interferon for MS Study Group 1999) demonstrated that even small doses of IFN-β1a (22 or 44 μg) administered once weekly influenced MRI evidence of disease activity. In this study, 293 relapsing–remitting patients randomized either to placebo or two doses of IFN-β1a were followed for 1 year. MRI features, combined unique lesions (showing either proton density/ T_2 or T_1 gadolinium activity) and lesion load, favoured the active treatment groups over placebo although clinical effects were not apparent at either dose. Resolving these issues of dose and frequency of administration has been the subject of several studies carried out since IFN-β1a and IFN-β1b were licensed (see below).

In the pivotal study of IFN-β1a (PRISMS; Prevention of Relapses and disability by Interferon-β1a Subcutaneously in Multiple Sclerosis 1998), 560 patients with relapsing–remitting multiple sclerosis with two or more episodes in the 2 years before (but not within 2 months of) treatment, and an EDSS score of 0–5, received IFN-β1a by subcutaneous injection (6 or 12 MIU) or a placebo preparation three times each week for 2 years. The primary outcome of this 2-year study was the relapse count over the course of the trial. Both doses were associated with a significant reduction in relapse rate compared with controls (1.82, 1.73 and 2.56 over 2 years, respectively; $p < 0.0002$), achieving about a 33% reduction (12 MIU compared with placebo) across the study period. The proportion of patients free from relapse during the 2 years of the study was 32% (12 MIU), 27% (6 MIU) and 16% (placebo) in the two treated groups and controls ($p < 0.005$ and $p < 0.05$, respectively). Both doses achieved a reduction in the severity of those relapses that did occur. Time to confirmed progression of >1 EDSS point increased in each group but, much as in the trials of IFN-β1b and other IFN-β1a preparations, this was less marked than the effect on relapse rate ($p < 0.04$: Figure 18.18). A novel composite score of integrated disability (amounting to the 'area under the EDSS curve over time') showed a 77% reduction in accumulated burden of disability during the study period. MRI was performed twice during the study and a subgroup underwent more frequent analyses. There was a reduction, by around 70% but higher in the more frequently studied cohort, in median number of active lesions per patient on each MRI scan in both treated groups compared with controls. Burden of disease increased by 11% in the control patients and decreased by 1% and 4% in the low-dose and high-dose groups, respectively ($p < 0.0001$).

The authors did not evaluate the success of blinding. As with other contemporary interferon studies, it is likely that patients were able correctly to guess whether they were receiving placebo or active therapy. Whether blinding was maintained for the evaluating physician was not reported. For reasons that remain unclear, the number of patients available for assessing the rate of nonprogression was only 76% of the study population at 1 year, and 70% at 18 months. Follow-up at the time of primary analysis was only 2 years. The authors reported 'confirmed worsening' at 3 months but did not present the data on 6 month and 12 month confirmed worsening. The analysis did not address the degree to which EDSS worsening attributable to relapse contributed to the data on sustained worsening.

An extension trial was started upon the completion of PRISMS. Patients originally receiving placebo were randomized to either low- or high-dose IFN-β1a. Those already receiving interferon continued on their original regimen of active drug (PRISMS Study Group 2001). Ninety per cent of the original 560 patients participated in the extension trial and almost 88% of this cohort completed the 2 year extension study.

The primary outcome in the extension study was relapse count per patient over the 4 years of the entire study. As such, the clinical behaviour (relapse count) in the first 2 years of the original study contributed substantially to the 4 year analysis of the extension. Not surprisingly, the extension trial demonstrated that IFN-β1a provides some protection (in terms of reduction in relapse rate) for those originally treated with placebo, although the trial was no longer blinded since patients and evaluators knew that all were receiving interferon therapy (Figure 18.19). Relapse rates over the 4 years of the study were 0.72 and 0.80 for the 12 MIU and 6 MIU groups, respectively, compared with 1.02 for the placebo patients who were randomized to 12 MIU at the time of the extension phase ($p < 0.001$ for both 'always interferon' groups compared with the group that started on placebo). There was a trend suggesting a marginal benefit for the higher dose of IFN-β1a ($p = 0.07$). Secondary analyses also showed a possible delay in time to confirmed progression for the high-dose group. MRI analyses supported a greater effect on lesion load for the high-dose group ('always 44 μg', 6.2% reduction; all other groups showed an increase in lesion load). Once again, the proportion of patients with neutralizing antibodies was higher in the low-dose group (23.8% vs. 12.5%) and, for the first time, the PRISMS investigators acknowledged that the presence of neutralizing antibodies reduced the clinical benefit on relapse rate (44 μg antibody-negative group, 0.50; 44 μg antibody-positive group, 0.81). In the analysis of this study, the authors did not correct statistically for multiple comparisons. The largest proportion of drop-outs was seen in the high-dose (44 μg) group (23%) – a finding that somewhat undermines confidence in these data. Analysis of the MRI results (Li and Paty 1999) confirmed the previously reported benefit on lesion load at 2 years (placebo, increase of 10.9%; 22 μg, decrease of 1.2%; 44 μg, decrease of 3.8%). Fifty per cent of placebo patients showed >10% increase in lesion load. Similarly, treatment reduced the frequency of active lesions (22 μg, 67% reduction; 44 μg, 78% reduction) and the proportion of patients with inactive scans (placebo, 8%; 22 μg, 19%; 44 μg, 31%). A subset of patients studied with more frequent MRI provided evidence that the treatment benefit could be identified as early as 2 months after starting interferon therapy. MRI atrophy was not evaluated.

As noted, the decision to include the 'relapse counts per patient' in the first 2 years of the original trial seems to have served the sponsor well in the extension phase, as did the accompanying editorial reporting that 'the placebo group never caught up' with the patients originally receiving interferon (Schwid and Bever 2001). This is hardly surprising. To catch up, the original placebo patients would either have had to be more responsive to the effects of interferon than those who were first randomized to the active agents, or the trial would have needed to be sufficiently sensitive to a loss of treatment effect in the third and fourth years of exposure. It is unlikely that the study was powered to demonstrate this effect. Lack of blinding in the extension study limits the conclusions that can be drawn from this phase of the trial considering the subjective nature of the primary outcome. The authors did not report on use of corticosteroids in the patients who changed treatments. Regrettably,

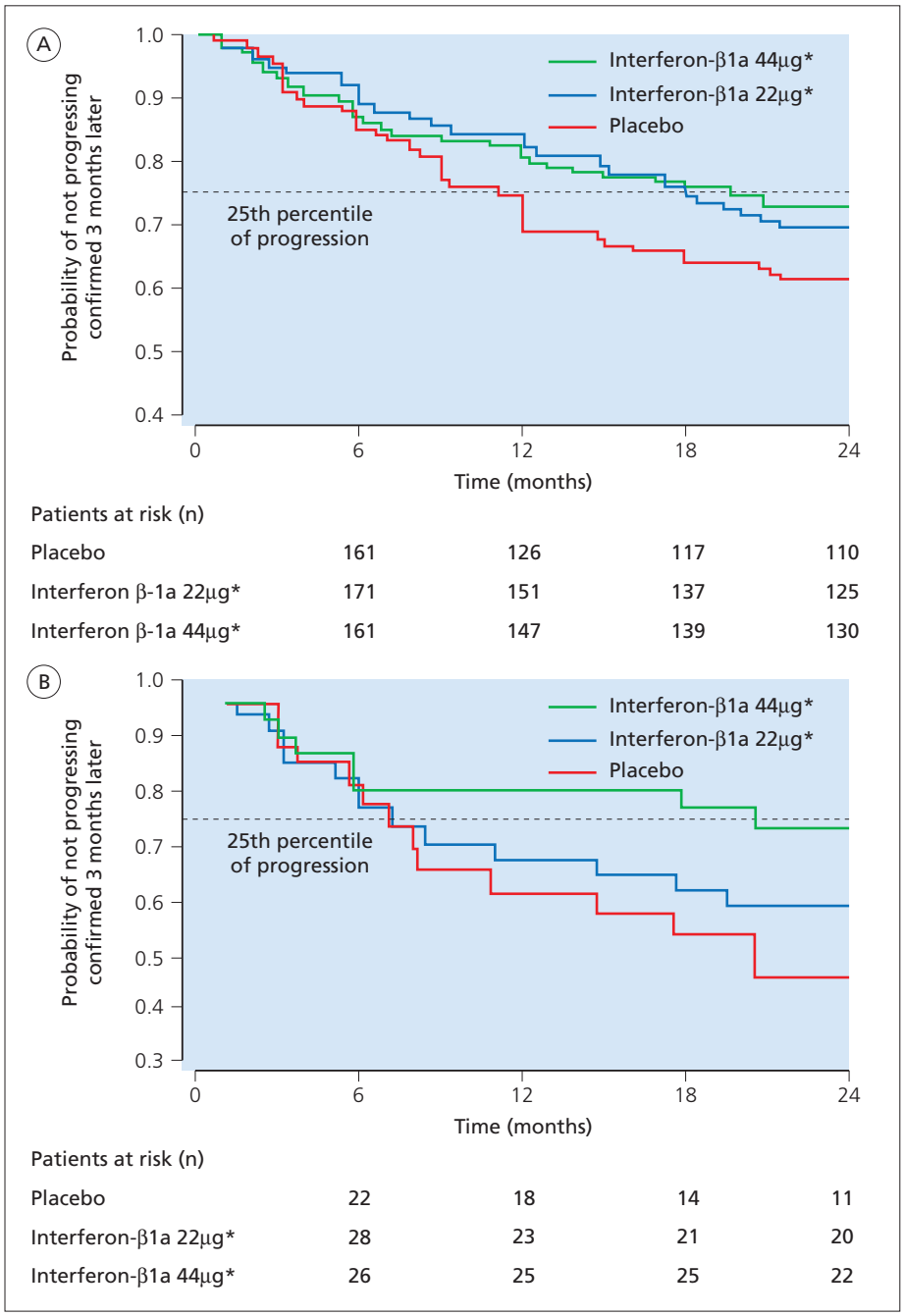


Figure 18.18 Treatment of relapsing–remitting multiple sclerosis with subcutaneous IFN-β1a (Rebif; PRISMS study). (A) Time to confirmed progression in disability in whole study group. (B) Patients with baseline EDSS >3.5. *$p < 0.05$ compared with placebo. Adapted from PRISMS Study Group (1998). © 1998, with permission from Elsevier.

this study demonstrates once again that multiple sclerosis disease activity continues despite treatment with interferons even at high dose.

Secondary progressive multiple sclerosis

Although there are many remaining questions surrounding the use of interferons in relapsing–remitting multiple sclerosis, there is at least a general belief that patients who choose to start therapy either with an interferon or glatiramer acetate (see below) can expect up to a 30% reduction in relapse rate over the initial 2 years on treatment. Treating physicians should indicate that there is no definite proof that treatment delays the development of persistent symptoms and signs. In secondary progressive multiple sclerosis, there is much less consensus on the short-term benefits of treatment. Although the interferons appear to reduce relapse frequency in the subset of individuals with secondary progressive disease who continue to experience attacks, it is hard to avoid the conclusion that clinical progression and MRI evidence of cerebral atrophy continue despite treatment. The published trials in secondary progressive multiple sclerosis are summarized in Table 18.5.

The European IFN-β1b study has been published in most detail (Kappos *et al* 1998; D.H. Miller *et al* 1999; Molyneux *et al* 2000). Thirty-two centres contributed 718 patients with secondary progressive multiple sclerosis (EDSS 3.0–6.5). Patients receiving active treatment demonstrated benefit for the primary outcome – time to worsening by 1.0 EDSS point confirmed at

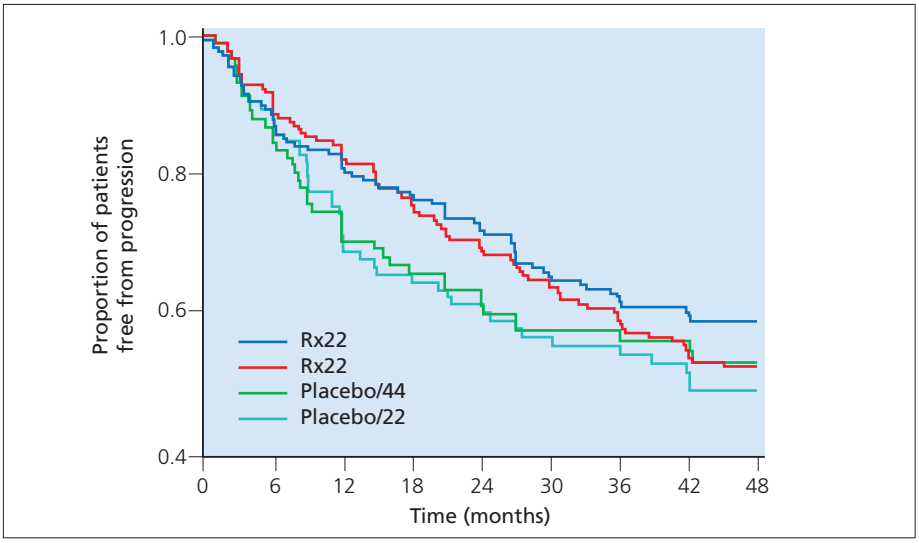


Figure 18.19 Treatment of relapsing–remitting multiple sclerosis with subcutaneous IFN-β1a (Rebif; PRISMS-4 extension study). Kaplan–Meier curves for time to confirmed progression in disability for years 1 through 4 (all patients). Proportions of patients are those free from progression. Adapted from the PRISMS Study Group (2001). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

Table 18.5 Recent randomized trials in secondary progressive multiple sclerosis

Trial (number enrolled; follow-up)	Treatment	Primary outcome	Secondary outcome	Comments
European IFN-β1b (718; 3 years)	8 MIU IFN-β1b by subcutaneous injection on alternate days vs. placebo	Time to EDSS worsening confirmed at 3 months (39% versus 50%; p = 0.0048). Probability of remaining progression-free noted by 1 year	Time to become wheelchair bound, hospitalizations, annual relapse rate, effect on MRI T_2 volume and activity. Time to 1.0 and 2.0 point EDSS change. Proportion with either relapses or progression	Year 3, increase of T_2 volumes in IFN-β-treated patients. Minor effect on preventing progressive cerebral atrophy
SPECTRIMS (618; 3 years)	22 μg or 44 μg IFN-β1a s.c. on alternate days vs. placebo	No effect on time to 3 month confirmed EDSS worsening (p = 0.88)	Treatment reduced relapse rate. Delayed progression in women at both doses. MRI effect seen on number of active lesions per patient per scan, combined unique activity and T_2 volume	Male placebo patients did unusually well. Patients with neutralizing antibodies showed no MRI effect
IMPACT (436; 2 years)	IFN-β1a s.c. 60 μg i.m. 1×/week vs. placebo	Benefit on MSFC noted in year 2	No effect on EDSS	MSFC not validated as disability measure
North American IFN-β1b (939; 3 years)	IFN-β-1b s.c. 8 MIU or 5 MIU/m^2 q2d vs. placebo	No effect on proportion with confirmed EDSS worsening	Positive effect on relapse rate, MRI activity and T_2 volume	No effect on EDSS
European mitoxantrone (188; 2 years)	5 or 12 mg/m^2 mitoxantrone every twelfth week vs. placebo (methylene blue)	Benefit on composite measure (EDSS, AI, SNS, time to first attack needing steroids, time to attack)	Number of patients with EDSS progression. Fewer new T_2 and Gd+ lesions	Outcome measure not validated, potential cardiotoxicity

GA = glatiramer acetate; Gd+ = gadolinium enhancing MRI lesions; IFN = interferon; EDSS = Expanded Disability Status Scale; MIU = million international units; AI = Ambulation index; SNS = Scripps Neurologic Scale; s.c. = subcutaneous; i.m. = intramuscular. Adapted from Noseworthy and Hartung (2003) with permission.

3 months (0.5 EDSS points, if baseline EDSS was 6.0 or greater; p = 0.0008). There was a 21.7% relative reduction in the proportion of patients reaching this outcome (placebo, 49.8%; IFN-β1b, 38.9%; p = 0.0048: Figure 18.20). This benefit was supported by an analysis of 6 month confirmed worsening, irrespective of whether patients lost to follow-up were counted as stable or worse (p = 0.0016). There was a difference in time to reach the primary end point between the two treatment arms of 9 months that first became apparent by survival analysis in the second year of treatment. A number of secondary outcomes also supported a treatment effect including time to unconfirmed wheelchair dependence (delayed by 9 months; and with a 32% reduction in the number of patients reaching this end point), progressive worsening without relapses, number of hospitalizations, annual

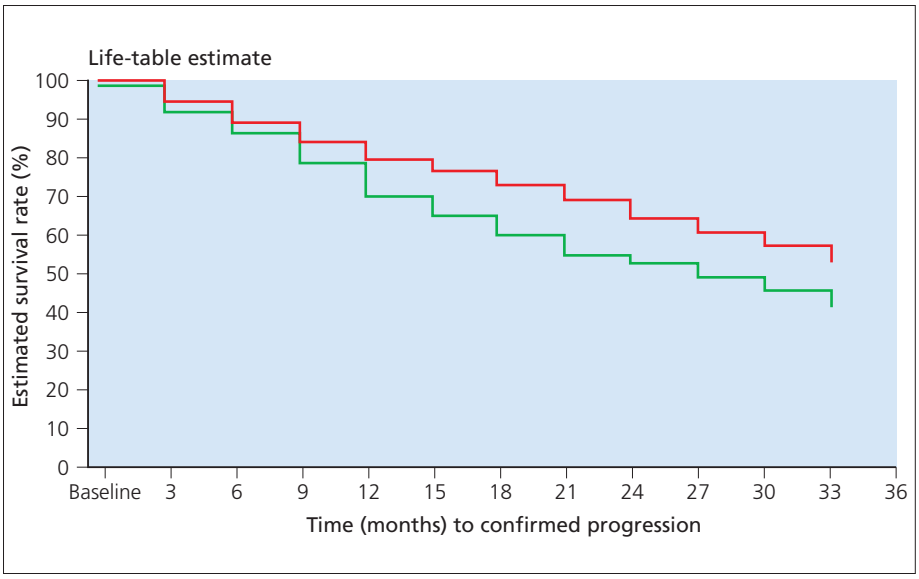


Figure 18.20 Treatment of secondary progressive multiple sclerosis with IFN-β1b. Time to confirmed progression at study termination (p = 0.007): green line = placebo (n = 358); red line = IFN-β1b (n = 360). Adapted from Kappos *et al* (2001). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

relapse rate, time to first relapse, proportion with moderate or severe relapses, and MRI T_2 volume (placebo, 8% increase; IFN-β1b, 5% reduction). An analysis of the 125 patients selected for frequent MRI studies (monthly scans between months 1 and 6 and 18 and 24) demonstrated fewer active scans early (65% reduction between months 1 and 6) and late in the study (78% reduction between months 18 and 24). The development of neutralizing antibodies in 27.8% of the IFN-β1b recipients reduced the benefit on relapse rate but not the disability findings (Polman *et al* 2003). Further analysis of the clinical findings reported a small number of patients lost to follow-up (48 of 358 placebo-treated patients; 40 of 360 patients given IFN-β1b). The proportion of patients with 3 month confirmed worsening of at least 2.0 EDSS points was reduced by 27% (p = 0.007). There was a 30% reduction in the proportion of patients either with fewer relapses or no progression (Kappos *et al* 2001). Subsequent analysis apparently confirmed that benefit from IFN-β1b was more likely in patients either with more than two pre-enrolment relapses or worsening of >1.0 EDSS points in the 24 months preceding randomization.

Two additional manuscripts detailed the MRI analysis of this large trial. It was reported by D.H. Miller *et al* (1999) that, at 3 years, there were persistent MRI lesion volume differences between the treatment arms (placebo, 16% increase; IFN-β1b, 2% decrease) although the MRI lesion volume increased for the first time in the IFN-β1b-treated cohort in the third year (p = 0.0001: Figures 18.21 and 18.22). Molyneux *et al* (2000), reporting on a subset of 95 patients in five centres that had MRI studies twice yearly during the 3 years of the study, found that atrophy continued in both treatment groups (placebo, 3.9%; IFN-β1b, 2.9% at 36 months). IFN-β1b treatment seemed to reduce the degree of atrophy developing in patients without evidence of contrast enhancing lesions at baseline (placebo, 5.1% loss of volume; IFN-β1b, 1.8%; p < 0.05: Figure 18.23). These atrophy studies, however, were underpowered because only 65 of 95 patients had the 3 year MRI scan.

The European study resulted in drug approval for the indication of secondary progressive multiple sclerosis in Europe although enthusiasm for its use varies widely amongst neurologists. The second large study of secondary progressive multiple sclerosis failed to confirm an effect on disability (SPECTRIMS; Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-β1a in MS: SPECTRIMS Study Group 2001). Failure of the other trials in secondary progressive multiple sclerosis to demonstrate a convincing benefit has influenced the degree to which this drug is used sparingly in clinical practice.

SPECTRIMS involved 22 centres in North America, Europe and Australia and included 618 patients with secondary progressive multiple sclerosis (baseline EDSS 3.0–6.5) randomized either to receive three subcutaneous doses of placebo each week or IFN-β1a (22 μg or 44 μg). The study failed to demonstrate a significant impact on the primary outcome measure (3 month confirmed EDSS worsening at 3 years; p = 0.146) although an early benefit was apparent at 1 year (Figures 18.24 and 18.25). Secondary analyses revealed the unexpected finding that the primary outcome was positive in female patients for both doses of IFN-β1a compared with placebo (22 μg, p = 0.036; 44 μg, p = 0.006). This may, in part, relate to the observation that men treated with placebo did unusually well (better than women treated with placebo). Interferon-treated patients with pre-enrolment relapses demonstrated a delay in time to progression. Treatment significantly reduced relapse rates (p < 0.001). Subsequent MRI analysis of SPECTRIMS (D.K. Li *et al* 2001) demonstrated a treatment effect on MRI parameters. Specifically, mean number of T_2 active lesions per patient per scan was reduced (placebo, 0.67; 22 μg: 0.20, 44 μg: 0.17, p < 0.001) as were monthly combined unique MRI activity (T_1 and T_2; p < 0.001) and accumulation of lesion load (baseline vs. 3 years; placebo, 10% increase; 22 μg, 0.5% decrease; 44 μg, 1.3% decrease; p < 0.0001). An effect of IFN-β1a was seen particularly in patients who reported relapses in the 2 years preceding randomization. The presence of neutralizing antibodies completely abrogated the evidence from MRI for a treatment effect in this trial.

The North American trial of IFN-β1b in secondary progressive multiple sclerosis is currently only published in abstract format (Goodkin 2000; see Table 18.5). Nine hundred and thirty-nine patients with secondary progressive multiple sclerosis were randomized either to receive placebo or one of two subcutaneous doses (8 MIU or 5 MIU per m^2) of IFN-β1b on

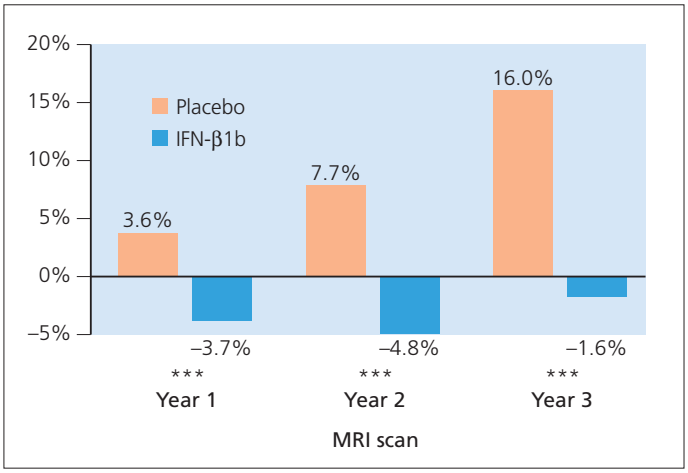


Figure 18.21 Treatment of secondary progressive multiple sclerosis with IFN-β1b. Annual MRI analysis. Percentage change in total lesion volume (TLV; mean) seen in the study cohort during years 1–3 compared with MRI scan at study entry. ***p < 0.0001 for difference between treatment groups. Adapted from D.H. Miller *et al* (1999). © 1999, reproduced with permission of John Wiley & Sons.

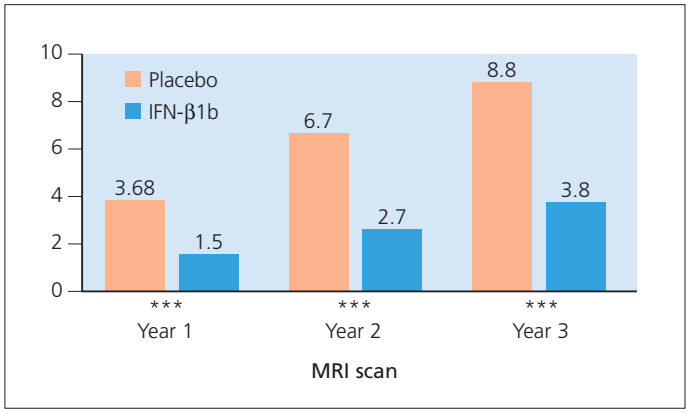


Figure 18.22 Treatment of secondary progressive multiple sclerosis with IFN-β1b. Annual MRI analysis. Cumulative number of active lesions (mean) seen in the study cohort during years 1–3 compared with MRI scan at study entry. ***p < 0.0001 for difference between treatment groups. Adapted from D.H. Miller *et al* (1999). © 1999, reproduced with permission of John Wiley & Sons.

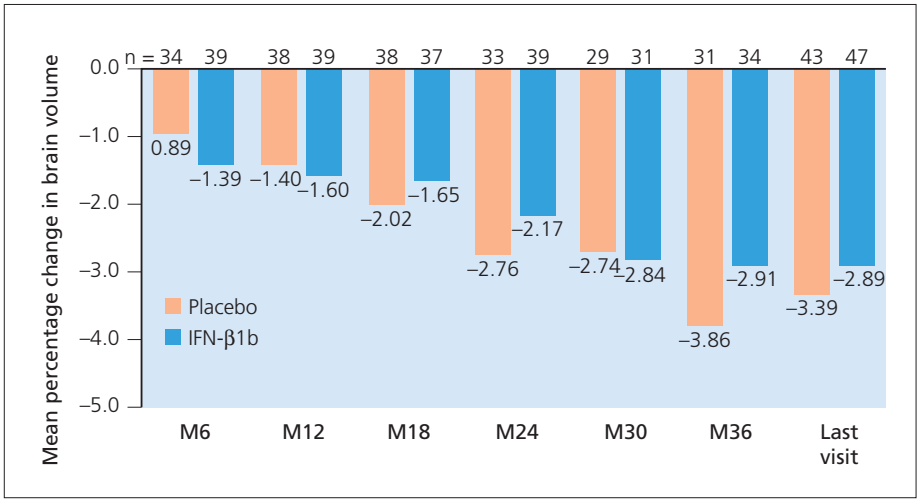


Figure 18.23 Treatment of secondary progressive multiple sclerosis with IFN-β1b. Percentage change in cerebral volume compared with baseline for all patients. M = month. Adapted from Molyneux *et al* (2000).

three occasions per week. The primary outcome (proportion of patients with confirmed EDSS progression at 3 years) was not reached although, as in SPECTRIMS, there were apparent treatment effects on relapse frequency and MRI measures (activity indices and T_2 lesion volume).

The final trial, of IFN-β1a in secondary progressive multiple sclerosis (IMPACT; International Multiple sclerosis secondary Progressive Avonex™ Controlled Trial; Cohen *et al* 2002) evaluated whether high dose (60 μg; compared with 30 μg used in relapsing–remitting multiple sclerosis) IFN-β1a given once weekly by intramuscular injection was more effective than placebo as measured by changes at 2 years in the MSFC. These investigators reported benefit using this 'more sensitive' but, as yet, incompletely validated outcome measure. Two components of the MSFC (the nine-hole peg test and the paced auditory serial addition task – PASAT) contributed to the positive findings in this trial (Figure 18.26). No benefit was seen in the timed gait or EDSS (secondary outcome). After reviewing these data, the FDA (United States) did not grant approval for once weekly IFN-β1a in secondary progressive multiple sclerosis.

Although much can be done to alleviate persisting symptoms (Chapter 17), the treatment of secondary progressive multiple sclerosis is largely unsolved. The classification of secondary progression is usually made retrospectively in a patient who, upon reflection, after a period of relapses with recovery appears to have worsened in recent months (years) either as a result of incomplete recovery from relapses or through a relapse-independent gradual decline in performance. In this context, the decision on whether or not to start (or continue) treatment is never easy and involves a careful discussion with the patient of expectations matched against the evidence available from published trials. The case for using IFN-β is perhaps most compelling for untreated patients who also report ongoing relapses. In this subset of patients, there is a good chance that treatment may reduce relapse frequency although the patient should be

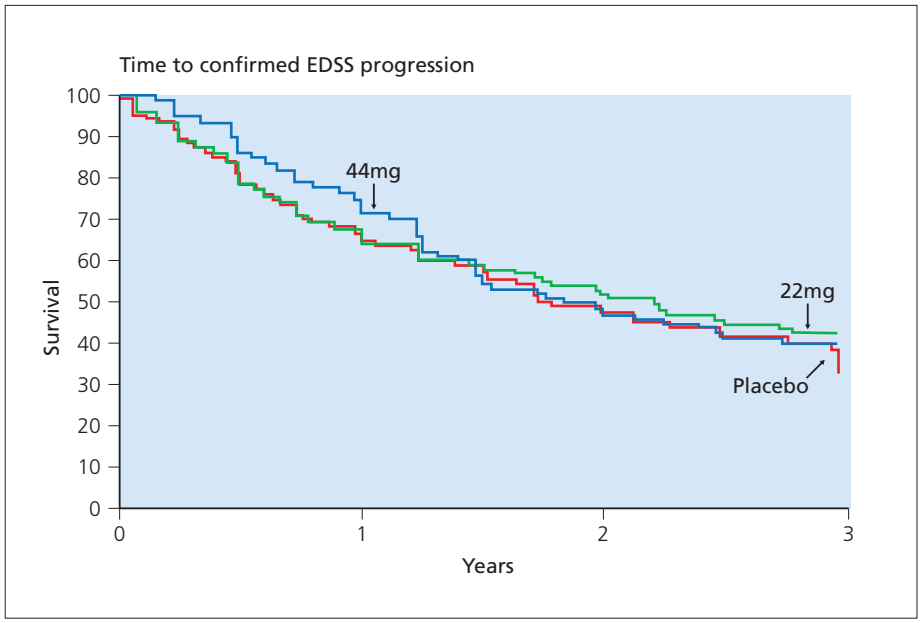


Figure 18.24 Treatment of secondary progressive multiple sclerosis with IFN-β1a subcutaneously three times weekly. Kaplan–Meier curves for time to confirmed EDSS progression for all patients. Adapted from SPECTRIMS Study Group (2001).

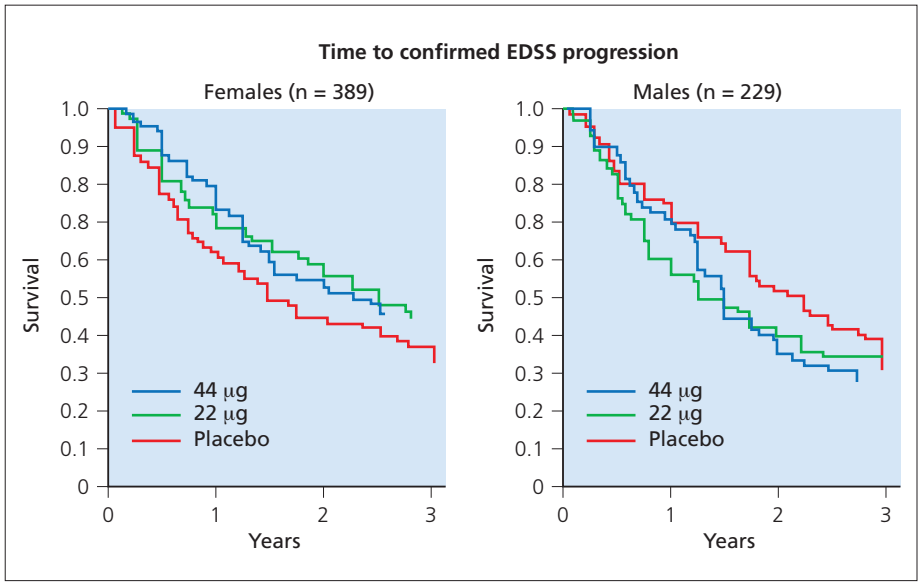


Figure 18.25 Treatment of secondary progressive multiple sclerosis with IFN-β1a subcutaneously three times weekly. Kaplan–Meier curves for time to confirmed EDSS progression for male and female patients. Adapted from SPECTRIMS Study Group (2001). © 2001, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

advised that attack rate and progression do not necessarily correlate. The situation is no more promising for people with primary progressive multiple sclerosis.

Primary progressive multiple sclerosis

Trials initiated before the mid1990s frequently failed to distinguish the various chronic progressive disease subtypes and primary progressive patients were lumped with those who once experienced or continued to suffer clinical relapses. In the absence of biomarkers to help determine that a therapeutic intervention is providing early benefit, treatment trials in primary progressive multiple sclerosis have relied upon changes in disability to determine efficacy (Neuhaus and Hartung 2001). Leary *et al* (2003) reported that IFN-β1a (30 μg and 60 μg weekly by intramuscular injection) was well tolerated at the lower dose but neither provided convincing evidence of benefit in a 2 year randomized, placebo-controlled, double-blinded trial of 50 patients with primary progressive disease. The lower dose may have marginally reduced T_2 lesion load accumulation but, paradoxically, measures of progressive brain atrophy appeared worse in those randomized to 60 μg weekly. Possibly this group had a greater lesion load at entry and, with a significant anti-inflammatory effect, the higher dose resulted in a more obvious reduction in brain volume.

Montalban (2004) has recently reported the preliminary analysis of a randomized, placebo-controlled phase two trial of IFN-β1b in 73 patients with either primary progressive or transitional multiple sclerosis. This preliminary report suggests that the IFN-β-treated patients demonstrated moderate benefits in the MSFC and MRI parameters (T_1 and T_2 lesion volume) at 2 years. The full report is awaited.

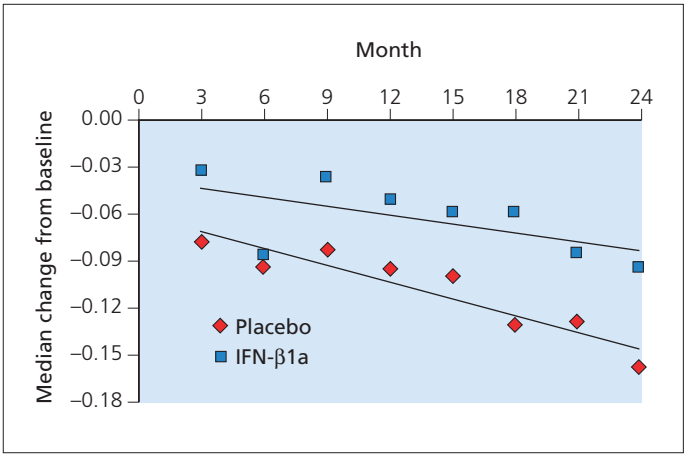


Figure 18.26 Treatment of secondary progressive multiple sclerosis with IFN-β1a by intramuscular injection once weekly. Median MS Functional Composite change from baseline every 3 months. The trend lines were determined by linear regression. Adapted from J.A. Cohen *et al* (2002). © 2002, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

Clinically isolated syndromes

Syndromes that may represent the inaugural episode in the natural history of multiple sclerosis have been the focus of subsequent attention with respect to disease-modifying treatments. Three reasons for this shift in attention can be suggested. First, the relative failure of IFN-β to influence features of multiple sclerosis, other than relapse rate, identifies the need to treat patients before the onset of disability and disease progression. Secondly, disease mechanisms that are predicted to be less responsive to cytokine therapy than inflammation are thought to increase with disease duration (see Chapter 10). Not only is there evidence from several sources that immune-mediated axonal injury is seen early in cases of relapsing–remitting multiple sclerosis but it also follows that early intervention with an anti-inflammatory agent might inhibit the cascade of events that leads to disease progression and thereby improve the long-term outlook. However, it should be pointed out that, whilst convincing for cases severe enough to warrant tissue examination, the same logic may not apply to more entrepreneurial examples of clinically isolated syndromes or relapsing–remitting multiple sclerosis. Thirdly, and to adopt a more entrepreneurial stance, early use of drug treatments makes good marketing sense, and each of these studies has been sponsored by pharmaceutical companies poised to benefit from prescribing drift.

Two recent randomized, double-blinded and placebo-controlled trials have addressed the issue of whether treatment with IFN-β1a at the time of presentation protects from recurrent clinical disease activity (Table 18.6). Fifty centres from the United States and Canada participated in the first of these two studies (CHAMPS; Controlled High risk subjects Avonex™ Multiple sclerosis Prevention Study; Jacobs *et al* 2000). Three hundred and eighty-three patients were randomized to receive either IFN-β1a at 30 μg weekly by intramuscular injection (n = 193) or a matched placebo (n = 190) for the duration of follow-up. Prior to starting active or placebo treatment, all patients were treated with methylprednisolone 1 g daily by intravenous injection for 3 days followed by 14 days of oral prednisone (1 mg/kg daily for 11 days then tapering in the final 4 days as follows – 20 mg on the first day, 10 mg on the second day, 0 mg on day three and 10 mg on the final day). Treatment commenced within 4 weeks from onset of the sentinel clinically isolated symptom. To be eligible, patients had to have two or more asymptomatic MR lesions on cranial imaging. Patients were assessed clinically at 4 weeks and every 6 months thereafter. The primary outcome measure was 'conversion to clinically definite multiple sclerosis (CDMS)' as defined by a further clinical relapse (Figure 18.27). When this occurred, patients were removed from the study and offered active treatment with IFN-β1a in an unblinded fashion. MRI studies were not performed at the time of putative conversion to multiple sclerosis. This high profile study was terminated early because of 'evidence for efficacy' in that fewer actively treated patients converted than controls ($p = 0.002$). At this point, 274 of the original 383 patients (71%) had completed 1 year of follow-up. We are struck by how quickly this study was brought to closure [of the 383 original subjects 210 (55%) were followed for 18 months; 131 (34%) were followed for 24 months; and only 61 (16%) were followed for 36 months]. Within months of publication, the United States FDA approved IFN-β1a for use in patients with clinically isolated syndromes deemed to be at high risk of developing multiple sclerosis.

The study bears further scrutiny. The trial was regrettably short, limiting the amount of available clinically relevant information. It is inconceivable that patients were blinded to the treatment received given the nearly universal occurrence of side effects from intramuscular administration of interferon. As such, patients receiving IFN-β1a would almost certainly have been aware that they were on active treatment, and vice versa. The possibility remains that incomplete blinding influenced the reporting of symptoms suggesting a first relapse. The primary outcome in this study was soft and merely required patients to identify symptoms suggesting a relapse. The conversion rate to clinically definite multiple sclerosis seems surprisingly rapid in CHAMPS (at 1 month: 18% in the placebo group vs. 9% of IFN-β1a-treated patients; and 26% compared with 12%, respectively, at 4 months). There have been many other examples where the placebo group did less well than expected thereby inflating the apparent treatment effect. The benefit of treatment in CHAMPS is less impressive if the patients who either converted or dropped out of the study and thereby could not benefit from treatment are considered together (44% of patients receiving IFN-β1a and 56% of the placebo group).

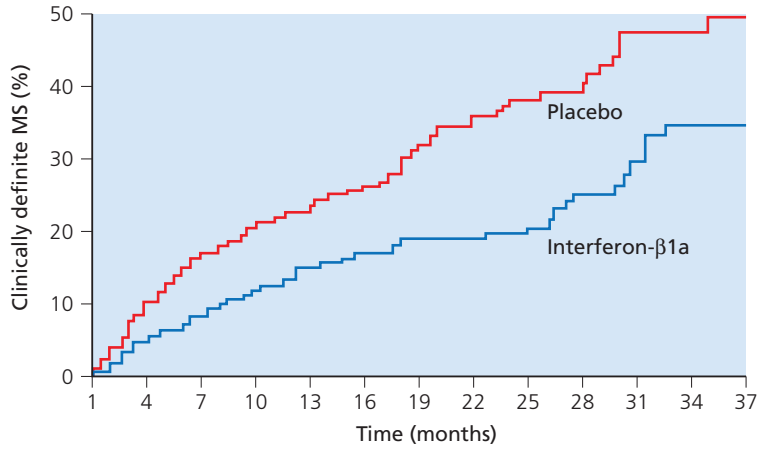
MRI data are presented as number of lesions rather than the proportion of patients showing MRI activity. The study design did not require MRI studies at the time of clinical conversion to multiple sclerosis. Furthermore, there are very few published clinical details and, as noted, no MRI data on two very important subsets of patients – the 46% of those enrolled who converted to clinically definite multiple sclerosis and the 15% who dropped out of the study. The absence of information beyond 18 months brings into question the durability of the effect on MRI features.

The relatively modest benefit of early treatment is perhaps seen more clearly in the observation from a subsequent paper that 50% of patients with clinically isolated syndromes treated with IFN-β1a demonstrated either clinical or MRI evidence of relapse while on treatment within the first 18 months of the study (R.W. Beck *et al* 2002: Figure 18.28). Additional analyses

Table 18.6 Recent randomized trials in clinically isolated syndromes

Trial (number enrolled; follow-up)	Treatment	Primary outcome	Comments
CHAMPS (383; 71% 1 year, 34% 2 year, 16% 3 year)	Corticosteroids, then: IFN-β1a 30 μg by intramuscular injection weekly vs. placebo	Delayed conversion to clinically definite multiple sclerosis (p = 0.002)	Patient unblinding likely. 'Soft' outcome measures. Limited follow-up. MRI only on 'stable' patients. No MRI studies beyond 18 months. Limited clinical data published
ETOMS (309; 2 year)	IFN-β1a 22 μg by subcutaneous injection once weekly vs. placebo	Delayed conversion to clinically definite multiple sclerosis (45% versus 34%)	Patient unblinding likely. 'Soft' outcome measures. Limited follow-up. MRI only on 'stable' patients. Not all MRI studies available for analysis of volume change

IFN = interferon. Adapted from Noseworthy and Hartung (2003) with permission.



Interferon-β1a group												
Number at risk	193	177	164	151	143	139	112	112	73	69	41	36
Clinically definite multiple sclerosis	9	6	7	5	3	4	0	2	4	3	3	0
Early withdrawal from study	7	7	6	3	1	4	0	1	0	0	0	1
Followed until end of study						19	0	36	0	25	2	1
Placebo group												
Number at risk	190	165	145	139	131	124	98	90	58	54	26	25
Clinically definite multiple sclerosis	18	13	7	4	6	8	6	3	1	6	0	1
Early withdrawal from study	7	6	0	4	1	1	1	5	0	2	0	0
Followed until end of study						17	1	24	3	20	1	0

Figure 18.27 Treatment of patients with clinically isolated syndromes and abnormal cerebral MRI with once weekly intramuscular IFN-β1a (Avonex; CHAMPS Study). Kaplan–Meier estimates of the cumulative probability of the development of clinically definite multiple sclerosis according to treatment groups. Adapted from Jacobs *et al* (2000). © 2000, with permission of the Massachusetts Medical Society.

have reported that IFN-β1a provides only partial (and we would suggest limited) protection regardless of the specific syndrome (optic neuritis, brainstem/cerebellar or cerebral involvement) and that risk of conversion to clinically definite multiple sclerosis is slightly greater for individuals with optic neuritis (R.W. Beck *et al* 2002), for patients with two or more contrast enhancing MR lesions, and for those already fulfilling MRI criteria for multiple sclerosis in this clinical context (Barkhof *et al* 1997a; CHAMPS Study Group 2002).

In a trial of similar design, the ETOMS (Early Treatment Of Multiple Sclerosis; Comi *et al* 2001a) investigators from 57 centres in 14 European countries randomized 309 patients having

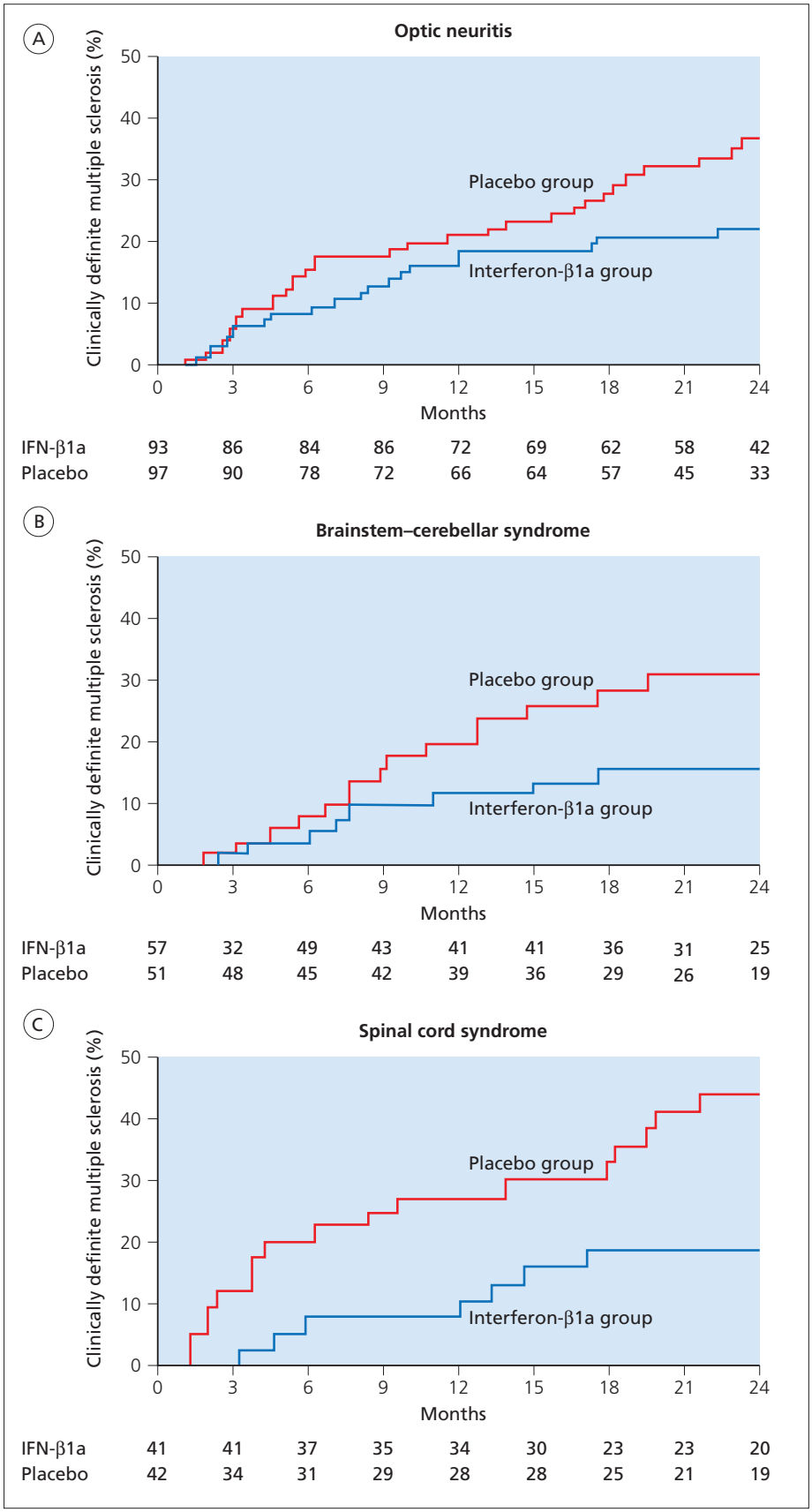


Figure 18.28 Treatment of patients with clinically isolated syndromes and abnormal cerebral MRI with once weekly intramuscular IFN-β1a (Avonex; CHAMPS Study). Cumulative probability of the development of clinically definite multiple sclerosis by treatment groups according to type of presenting event. (A) Optic neuritis; (B) Brainstem–cerebellar syndrome; (C) spinal cord syndrome. Adapted from Beck *et al* (2002). © 2002, reproduced with permission of John Wiley & Sons.

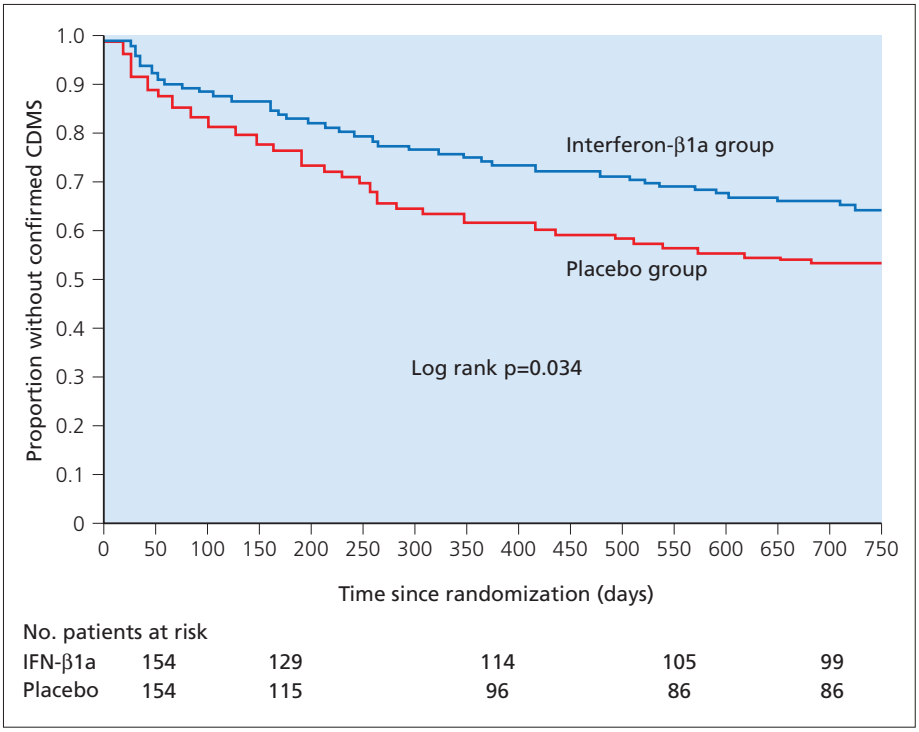


Figure 18.29 Treatment of patients with clinically isolated syndromes within the last 3 months and abnormal cerebral MRI with once weekly subcutaneous IFN-β1a (Rebif; ETOMS Study). Kaplan–Meier survival curve of probability of no conversion to clinically definite multiple sclerosis over 2 years. Adapted from Comi *et al* (2001a). © 2001, with permission from Elsevier.

clinically isolated syndromes within the previous 3 months if they had four or more MRI lesions, to receive either once weekly low dose (22 μg) IFN-β1a subcutaneously or a matched placebo. Patients were assessed clinically at 1 month and then every 6 months for 2 years, with annual MRI scans. Ninety per cent completed follow-up. At 2 years, the authors claimed a treatment advantage with 45% of placebo-treated patients converting to multiple sclerosis compared with 34% of those receiving IFN-β1a (Figure 18.29). As with CHAMPS, no attempt was made to determine the success of blinding in this trial. In a subsequent manuscript, Filippi *et al* (2004b) reported an apparent benefit on the development of brain atrophy at 24 months in the treated group (30% reduction in the observed decrease in brain volume; –1.18% IFN-β1a vs. –1.68% for the placebo group; $p = 0.0031$). It remains to be determined whether this very small weekly dose of interferon offers an important and potentially long-term benefit. Indeed, the degree of atrophy is so small in the untreated patient (<2% of normalized brain parenchymal volume) that it stretches the imagination to accept that a 30% reduction in this metric will be biologically meaningful in this chronic disease. Accordingly, in an accompanying editorial, D.H. Miller (2004a) offers optimism for genuine protection from irrreversible brain injury but cautions that it remains to be confirmed that this effect on brain atrophy will translate into delayed or reduced disability.

The same concerns arise with respect to the subjective primary outcome measure as in CHAMPS. The frequency with which the MRI studies of asymptomatic patients showed evidence of recurrent disease activity (MRI conversion) has not been published but there are differences between the trials. The patients in ETOMS had a high frequency (39%) of multifocal symptoms at onset (compared with 0% in CHAMPS). The ETOMS patients, therefore, were at approximately a two-fold increased risk of converting to multiple sclerosis in a short time frame. Additionally, the longer interval between symptom onset and entry in the study (3 months vs. 1 month for CHAMPS) probably increased the conversion rate in ETOMS. Only 70% of participants in ETOMS received corticosteroids at the time of randomization compared with 100% in CHAMPS. Despite their limitations, these studies provide evidence that early treatment with IFN-β1a may have a partial, and at least short-term, benefit in delaying further episodes of demyelination either in patients at risk of multiple sclerosis or in those already established in the early stages of the illness. We emphasize again the obvious need to determine whether any of these therapies provides a treatment benefit that is sustained over a prolonged period and is clinically useful. In part, this reflects the lack of robust mechanisms for evaluating the long-term benefits of treatment but it is an enormously important question since there are theoretical benefits in strategies that arrest axonal injury before it has contributed to the progressive and presumably irreversible axonal degeneration that underlies the later stages of multiple sclerosis.

Using a whole brain ratio method, brain atrophy was assessed over 2 years in a placebo-controlled trial of IFN-β1a in relapsing–remitting disease (C.K. Jones *et al* 2001). Atrophy measures were available in 519 patients, 172 of whom were on placebo treatment. Significant brain atrophy was seen in the total cohort. Whole brain ratio at baseline correlated weakly with T_2 lesion load and decreased by 1.4% over 2 years but no difference in the rate of atrophy was seen between treatment arms. Cerebral atrophy has been evaluated in 52 relapsing–remitting patients for 6 months before and 24 months following treatment with IFN-β1a, and correlated with other MRI lesion and clinical parameters (Gasperini *et al* 2002). During the 2 years of

treatment, there was a significant reduction of brain volume (mean –2.2%) that correlated weakly with the mean number of enhancing lesions on 6 monthly pretreatment scans. Over the 2 years, 26 patients exhibited significant atrophy and 26 did not. Of the former, 13 experienced an increase in disability whereas only three of the latter became more disabled. This confirms other studies showing a link between increasing atrophy and disability (Losseff *et al* 1996b; Paolillo *et al* 1999). In a 2 year placebo-controlled trial of IFN-β1a in relapsing–remitting multiple sclerosis, atrophy was measured from yearly scans using brain parenchymal fraction. The mean decrease was similar in both arms in year one, but smaller in the IFN-β1a arm in year two (Rudick *et al* 1999). The changes in brain parenchymal fraction during this 2 year period showed little or no correlation with lesion measures. There was c.1% loss of central cerebral volume per year in both the treated and placebo arms. Prolonged 8 year follow-up of the placebo cohort from this trial assessed the long-term relationship between earlier brain parenchymal fraction change and later disability (E. Fisher *et al* 2002). Comparison of quartiles based on change over the first 2 years revealed a greater likelihood of developing severe disability (EDSS ≥ 6 at follow-up) in patients with most atrophy during the initial 2 years.

Devic's disease (neuromyelitis optica)

As discussed in Chapter 16, the treatment of acute symptomatic neurological syndromes in patients with Devic's disease (neuromyelitis optica) is essentially the same as for multiple sclerosis in relapse. A significant proportion of these patients relapse and stepwise worsening may lead to severe and irreversible neurological disability, often with troublesome pain (Wingerchuk *et al* 1999; Wingerchuk and Weinshenker 2003). Some patients have a malignant course with early disability or shortened life expectancy.

There is limited published experience to guide treatment decisions. There are no proper, phase III randomized trials on which to make evidence-based decisions. Karussis *et al* (1998) have recommended that antiplatelet agents or anticoagulants be used to treat patients with Devic's disease if anti-phospholipid antibodies are present. Mandler *et al* (1998) published an uncontrolled series of seven patients, reporting that long-term oral prednisone and azathioprine may stabilize the course of neuromyelitis optica for a period of up to 18 months. Patients were initially treated with intravenous methylprednisolone (500 mg twice daily) for 5 days and then started on oral prednisolone (1 mg/kg). Prednisone was gradually tapered and then converted to an alternate day schedule, and continued for the full 18 months; on day 21, oral azathioprine was begun at 2 mg/kg. Clearly, confirmatory studies are needed. Anecdotal experience suggests that IFNs are not effective and, theoretically, glatiramer acetate might be contraindicated given the possibility that enhanced Th2 activity would be expected to worsen a humorally mediated disorder such as Devic's Disease (Duda *et al* 2000; Gold and Linington 2002). With recent publications describing antibody- and complement-dependent effector mechanisms of tissue injury (Lucchinetti *et al* 2002) and response to plasma exchange (Keegan *et al* 2002), it seems increasingly likely that immunosuppressive strategies focusing on reducing B-cell function should take preference in seeking to build on immediate improvements (see Chapter 16) and stabilize the longer-term clinical course. Cree *et al* (2005) administered rituximab, a chimeric murine/human monoclonal antibody that binds to the CD20 antigen and depletes B cells, to eight patients with Devic's disease in an open label, pilot trial. Treatment was well tolerated and seemed to suppress relapses. The treated patients generally improved (seven of eight) but – as the authors acknowledge – in the absence of controls, recovery might have been spontaneous. Lennon *et al* (2004) identified a serum autoantibody that may contribute to diagnostic certainty in the evaluation of Devic's disease (see Chapter 7). This IgG antibody has now been shown to bind to the aquaporin-4 water channel suggesting that Devic's disease may be an autoimmune channel disorder (Lennon *et al* 2005). This bioassay should enhance efforts to describe the full clinical spectrum of neuromyelitis optica and hasten the discovery of key antigens involved in triggering the disease and maintaining disease activity.

Dose effects and comparison of different interferons

Placebo controls were uniformly used during the early period of clinical trials of interferons in multiple sclerosis. There were no 'head-to-head' studies comparing the relative efficacy of different drugs, doses and routes of delivery. This situation has subsequently changed (Table 18.7). Several direct comparisons of licensed and unlicensed products are available and more are under way. It is apparent, and in the main regrettable, that these studies are motivated primarily by competition for market share. Will they provide novel insights that lead to better treatment strategies?

The pivotal trials led to much speculation about the relative merits of subcutaneous injections of IFN-β1b three times weekly compared with the more convenient schedule of giving IFN-β1a by the intramuscular route once each week. The North American IFN-β1b trial showed that alternate day treatment reduced relapse rates by 28–33% in each of the first 3 years of use, and clearly demonstrated a dose effect. The pivotal IFN-β1a study did not report a reduction in relapse rate over the first year, and had a lesser effect in the second than already reported for IFN-β1b, yet it was granted approval by the FDA (United States) for its claim to reduce disease progression. Much like the pivotal North American IFN-β1b trial, PRISMS and SPECTRIMS indicated that a higher dose of interferon was perhaps more effective in reducing relapses than a lower dose when each was administered three times weekly. A study evaluating two doses (30 and 60 μg) of once weekly intramuscular IFN-β1a failed to support a dose effect except for MRI outcomes during the third year (Clanet *et al* 2002). Clanet *et al* (2004) extended the opportunity to these patients to remain on the same dose of IFN-β1a for up to 4 years (56% of the original cohort had completed 4 years of treatment at the time of publication). Again, clinical outcomes were similar between the two groups (30 μg or 60 μg weekly). The Once Weekly Interferon for Multiple Sclerosis Study (OWIMS 1999) showed that a higher dose of once weekly IFN-β1a influenced MRI features more than a lower dose, although neither had a convincing effect on clinical outcomes. Eighty-four percent of the OWIMS subjects agreed to remain on study for the duration of a 4 year extension trial. Freedman *et al* (2005b) reported that once

Table 18.7 Recent randomized trials in relapsing–remitting multiple sclerosis

Trial (number enrolled; follow-up)	Treatment	1° Outcome	Comments
North American GA Extension Study (208; up to 6 years)	Glatiramer acetate 20 mg subcutaneous daily daily injection	Annual relapse rate: reduction reported	Patients enrolled in extension trial had fewer relapses and disability worsening than non-participants. Historical control group contained progressive patients
European-Canadian GA (239; 9 months)	Glatiramer acetate 20 mg subcutaneous daily injection vs. placebo	Total number of Gd+ lesions (29% reduction, p = 0.003)	Delayed, partial benefit: first seen by 6 months and many new lesions in GA group; proportion of patients with Gd+, T_1 black hole lesion volumes not significant and T_2 volumes continue to increase. Short follow-up
PRISMS-4 (506; 90% of initial study; 2 + 2 years)	After 24 months, placebo patients randomized to 22 μg or 44 μg IFN-β1a by subcutaneous injection × 3/week	Relapse count over 4 years (p = 0.001)	Unusual primary outcome; no chance for placebo cases to catch up; largest drop-out in 44 μg group. No adjustment for multiple comparisons. Almost achieves a benefit on disability benefit but effect is modest
INCOMIN (188; 1 year)	IFN-β1a 30 μg by intramuscular injection × 1 per week vs. 9 MIU IFN-β1b by subcutaneous injection on alternate days	Months 6–12, IFN-β1b superior reduction in relapse rate, proportion relapse-free and EDSS	Only radiologist blinded
EVIDENCE (677; 6–12 months)	IFN-β1a 30 μg by intramuscular injection × 1 per week vs. 44 μg by subcutaneous injection × 3 per week	Proportion relapse free favours high dose (75% vs. 63%)	Efforts to blind the evaluators but not patients. Short duration hard to evaluate
Tysabri (213; 1 year)	Tysabri 3 or 6 mg/kg by intravenous injection × 1 per month vs. placebo once per month	Fewer Gd+ lesions (p < 0.0001)	Effect disappeared when treatment stopped. Safety concern when given with IFN-β1a

Gd+ = gadolinium enhancing MRI lesions; IFN = interferon; EDSS = Expanded Disability Status Scale; MIU = million international units; Tysabri = humanized monoclonal anti-α_4 integrin antibody. Adapted from Noseworthy and Hartung (2003) with permission.

weekly IFN-β1a retains a slightly positive MRI effect with no clinical benefit in patients with relapsing–remitting multiple sclerosis. The results of recent direct comparisons (INCOMIN and EVIDENCE, see below) have been used to strengthen the claim that, although less convenient, exposure to interferon three times weekly outperforms weekly administration, at least for the first 6–12 months of treatment.

The INCOMIN study (Independent Comparison of Interferon Trial) randomized 188 relapsing–remitting patients with multiple sclerosis from 15 centres in Italy either to once weekly intramuscular IFN-β1a or alternate day subcutaneous injections of 8 MIU IFN-β1b, under single-blind (evaluator) conditions (Durelli *et al* 2002). The primary outcome measures were the proportion of relapse-free patients, and no new MRI lesions at 2 years. Both primary outcomes favoured the alternate day dose of IFN-β1b, and the magnitude of the effect became more evident in the second year of study (Figure 18.30).

In the EVIDENCE (Evidence of Interferon Dose–response: European North American Comparative Efficacy) trial, investigators from 56 centres in Europe and North America completed a randomized study directly comparing once weekly intramuscular IFN-β1a with high-dose subcutaneous (44 μg) three times weekly IFN-β1a in 677 patients with relapsing–remitting multiple sclerosis each having a baseline EDSS of <5.5 (Panitch *et al* 2002). This study was powered to demonstrate a treatment difference within the first 6 months of follow-up. The patients were not blinded but evaluators of clinical and MRI outcomes were unaware of the treatment randomization. The primary outcome was the proportion of relapse-free patients at 6 months, although patients were also evaluated at 1 year. At both 6 and 12 months patients receiving three times weekly IFN-β1a were more likely to be relapse free and with a reduced number of active MRI lesions (Figure 18.31). Fewer patients in the once weekly group developed neutralizing antibody (2% vs. 25%) and injection site reactions or liver enzyme elevations were also less frequent. Long-term safety data at ≥64 weeks confirmed that adverse events were more frequent with the high-dose group and were mainly attributable to the frequency of injection site reactions and hepatic and haematological abnormalities. Objectively, most events were rated as mild, and more serious adverse effects were equally distributed between groups (Sandberg-Wollheim *et al* 2005).

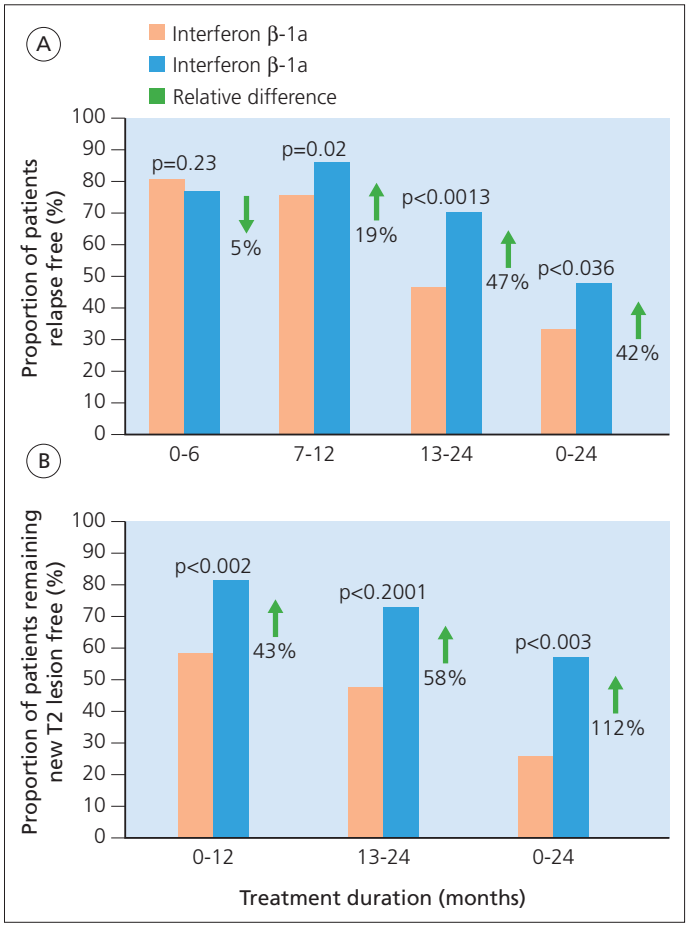


Figure 18.30 Treatment of relapsing–remitting multiple sclerosis either with every other day subcutaneous IFN-β1b or once weekly intramuscular IFN-β1a (INCOMIN study). (A) Relative difference (proportion in IFN-β1b group minus proportion in IFN-β1a group divided by proportion in IFN-β1a group) between the proportion of patients free from relapses. (B) New proton density or T_2 MRI lesions in the treatment groups at different time points. Adapted from Durelli *et al* (2002). © 2002, with permission from Elsevier.

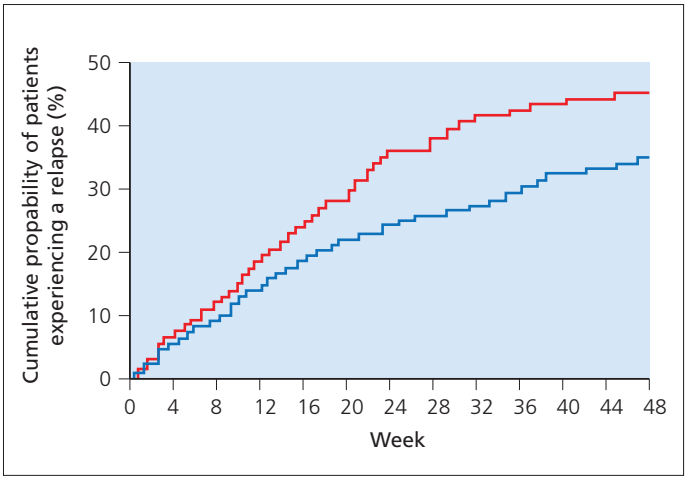


Figure 18.31 Treatment of relapsing–remitting multiple sclerosis either with three times weekly subcutaneous IFN-β1a (Rebif; blue line) or once weekly intramuscular IFN-β1a (Avonex; red line; EVIDENCE Study). Kaplan–Meier curves illustrating the cumulative probability of patients experiencing a first relapse during the study. Adapted from Panitch *et al* (2002).

Proponents of once weekly interferon hold that the findings of these trials are suspect since in neither study were patients blinded to the treatment assignment. As has been the case with all trials performed to date, there is no mechanism in place adequately to define the long-term implications of these early efficacy claims, or the potential that neutralizing antibody formation will eventually compromise any treatment effect on disability. In 2004, more patients were receiving once weekly intramuscular IFN-β1a than other preparations – primarily because of convenience and more effective sponsor marketing, but also through physician preference given the lower incidence of neutralizing antibody formation and FDA approval for the putative reduction in disability.

The first systematic Cochrane review of interferons in relapsing–remitting multiple sclerosis appeared in 2003 (Filippini *et al* 2003a). The authors concluded that there was evidence only for a reduction in relapse frequency during the first year of treatment with no convincing benefit thereafter, and no effect on disability (Figures 18.32 and 18.33). As expected, this publication triggered considerable editorial discussion and correspondence centred, in large part, on methods used to conduct the systematic review (such as handling of drop-outs, comparability of studies, lumping trials of IFN-α and IFN-β, and ignoring MRI effects; Filippini *et al* 2003b; 2003c; M. Freedman *et al* 2003; Goodin 2003; Kappos and Kesselring 2003; Paty *et al* 2003; Rudick *et al* 2003). As with mitoxantrone, independent calculation of the 'number needed to treat' measure from each of the published trials turns out to be somewhat discouraging (Figure 18.34). In the setting of patients presenting with a clinically isolated syndrome, seven must be treated to prevent one patient developing clinically definite multiple sclerosis at 3 years. In the setting of relapsing–remitting multiple sclerosis, nine have to receive interferon for 1 year to prevent a single relapse, and eight patients must be treated for 2 years to prevent one patient from worsening by a single EDSS point. Although these numbers needed to treat may actually be superior to those quoted for other chronic medical conditions (see Sackett *et al* 2000), the high cost of interferon therapies and the apparent enthusiasm for their widespread use justify some reflection on cost–benefit ratios and health care economics. In a recently published systematic review, Rice *et al* (2005) concluded that the IFNs provide modest reduction in relapse risk for up to 2 years but there is insufficient evidence to judge efficacy beyond this time point. As with every systematic review, much hinges on an estimate of the behaviour of those lost to follow-up. In this example, if – to take a worst case – IFN-treated drop-outs worsened, the statistical benefit of treatment would no longer be judged significant.

Adverse effects

In the pivotal trials, blinding was not thought to have been undermined by the local or systemic effects of subcutaneous IFN-β1b but was maintained less well in patients receiving intramuscular IFN-β1a (Avonex; 32% of patients were unblinded but the number of placebo cases correctly guessing the treatment code was not recorded). Now, several years on and with more

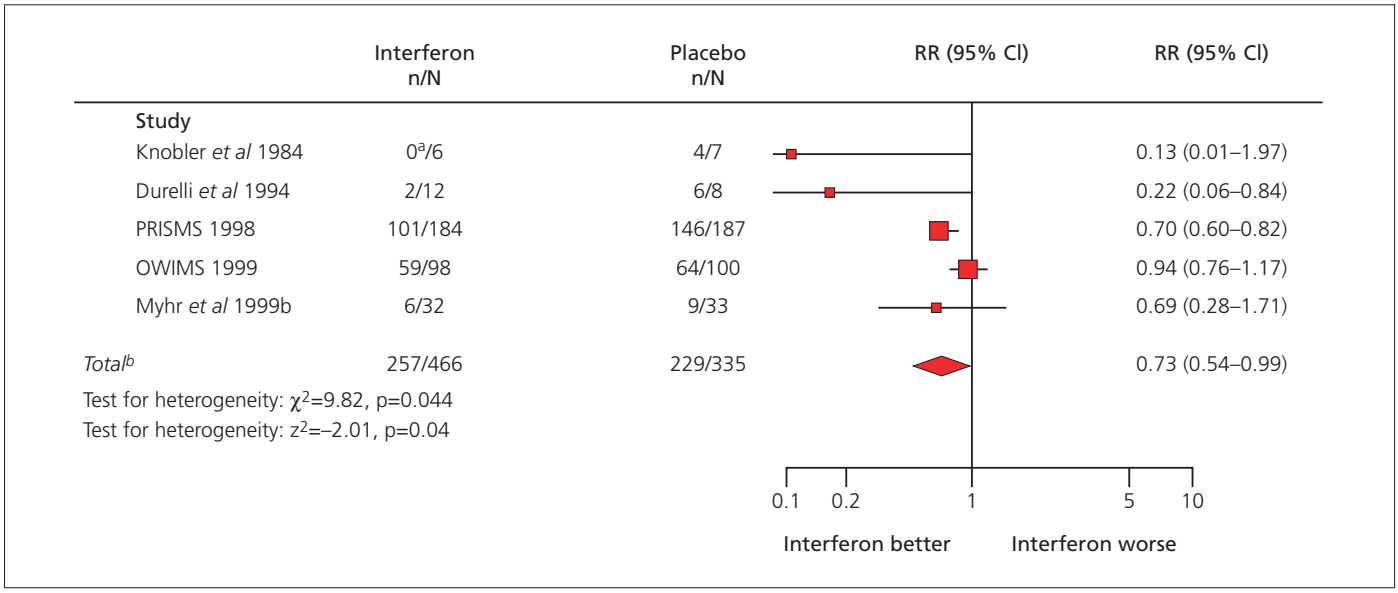


Figure 18.32 Meta-analysis of patients who had at least one exacerbation during the first year of treatment. n/N = number of patients who had exacerbations/number of patients randomized. To estimate relapse rate, 0.5 was added to each cell of the 2 × 2 table for the trials. a = no patients with exacerbations in the IFN group; b = random effects model. Adapted from Filippini *et al* (2003a).

experience of these agents, we doubt that patients can be adequately blinded to the side effects of interferons. The main adverse effects of IFN-β1b and IFN-β1a are local injection site reactions (Figure 18.35), flu-like symptoms and hyperthermia at onset, and depression. Fortunately, there is no significant drug hypersensitivity. Based on the evidence from clinical trials, contraindications to the use of IFN-β are pregnancy, epilepsy and depression. Post-marketing experience in the United States indicates that patients in whom fatigue and depression occur prior to starting IFN-β1b, especially those with secondary progressive disease, often abandon treatment because of adverse effects (Neilley *et al* 1996). Events may be delayed for up to 29 months and usually consist of injection site reactions (Gaines and Varrichio 1998). The long-term risks of IFN-β1b are unknown.

With time, most patients are better able to tolerate the adverse effects commonly associated with the use of IFN-β (Walther and Hohlfeld 1999). Injection site reactions are more frequent with subcutaneous than intramuscular administration. These may become intolerable leading to discontinuation of treatment. Careful attention to technique (avoiding intradermal injections, excessive sun exposure, overly cooled solutions and nonsterile technique) and local icing of the injection site may help. Necrosis at the injection site is more common in women, especially if the medication is not warmed to room temperature before injection. Intramuscular injections seldom cause tissue reactions but abscess formation, although rare, may lead to significant morbidity. Many patients are able to tolerate the transient flu-like symptoms that frequently occur for the first 4–12 hours after each injection by administering the dose in the evening along with an oral anti-inflammatory agent (acetominophen or ibuprofen: G.P. Rice *et al* 1999; Rio and Montalban 2000). Occasionally it may be necessary to reduce the dose of interferon and to co-administer oral prednisone for a few weeks to improve compliance (Rio *et al* 1998). Patients often develop transient elevations of liver function tests, neutropenia and, less commonly, anaemia requiring dose reduction or a drug holiday.

We routinely measure liver function and a full blood count at baseline, after the first week and month of exposure and then every 3 months thereafter. Menstrual function may be affected, usually resulting in menorrhagia. The issue of depression remains controversial. We generally advise patients and family members that interferons may either expose or worsen underlying depression. They should remain alert to a change in mood that may require treatment. There are reports that spasticity may increase with interferons (Bramanti *et al* 1998; Frese *et al* 1999). Occasionally treated patients develop serological abnormalities suggesting the induction of autoimmunity, including antibodies to thyroid, nuclear and muscle antigens. There are several reports of treatment-induced thyroid dysfunction associated with the use of IFN-β in multiple sclerosis. The initial reported frequency varied from 0% to 34% (Colosimo *et al* 1997; Durelli *et al* 1998; 1999; Kivisakk *et al* 1998c; Monzani *et al* 1999; 2000; Rotondi *et al* 1998; Schwid *et al* 1997a). These trials involved small cohorts of patients treated for varying durations, and to us the overall estimated prevalence (23%) seems high based on personal experience, although that there is a genuine relationship is unambiguous (see below). A more recent study followed 106 patients receiving IFN-β for between 31 and 84 months (Caraccio *et al* 2005). Thyroid autoimmunity affected one-quarter of the patients. The majority were examples of hypothyroidism, half of which were transient. Hyperthyroidism occurred in one-fifth of the cases, and was always characterized by an initial hyperthyroid phase, followed by a plateau culminating in hypothyroidism. It also was often subclinical or transient. Clinical thyroid disease and the development of thyroid autoantibodies in isolation occurred most commonly in the first year after treatment. Females were preferentially affected, but thyroid disease was more persistent in males. The presence of thyroid specific antibodies at baseline (8.5%), the presence of subclinical hypothyroidism prior to

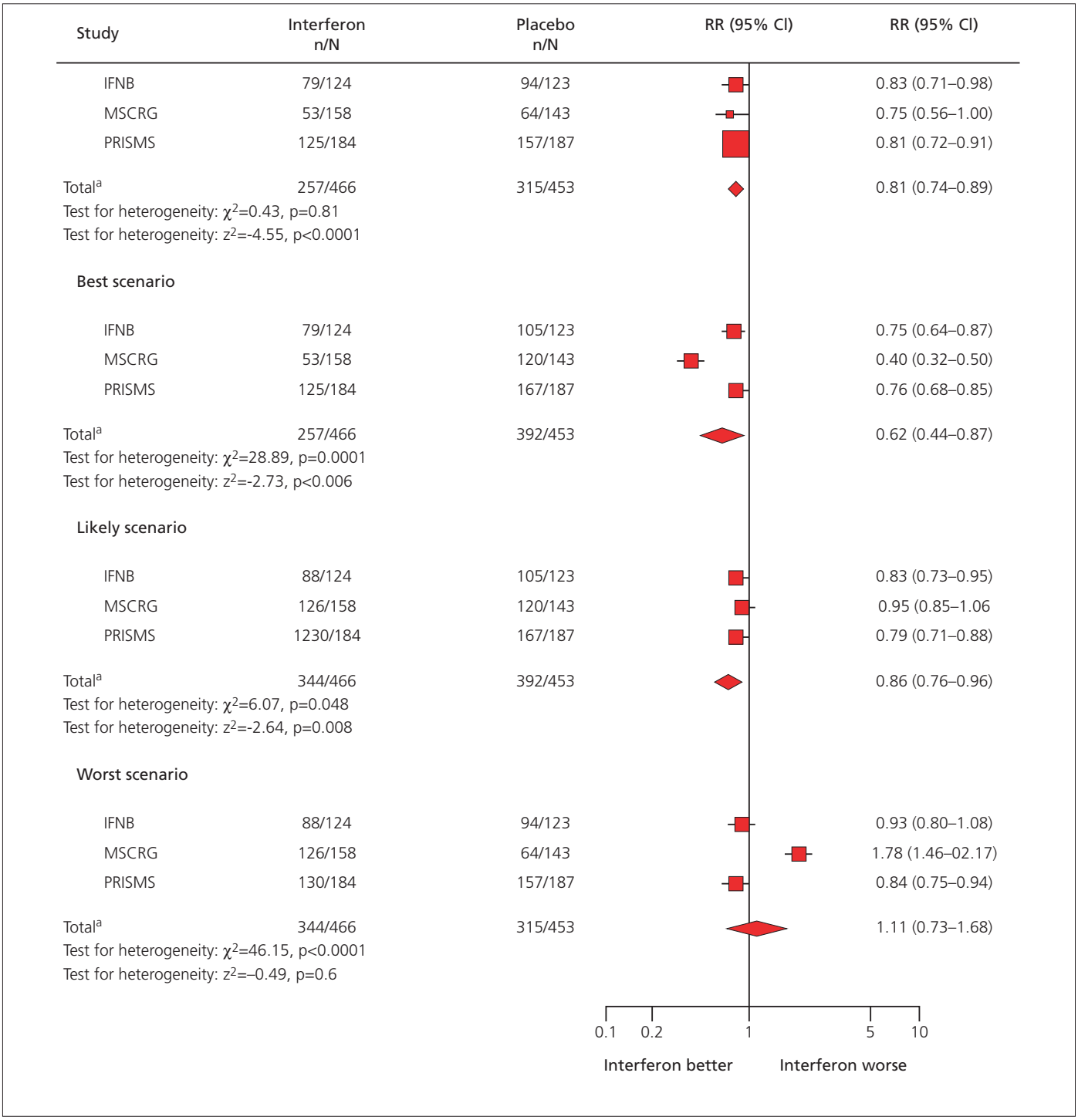


Figure 18.33 Meta-analysis of patients who had at least one exacerbation during the first 2 years of treatment. n/N = number of patients who had exacerbations/number of patients randomized. a = random effects model. References: IFNB = IFNB Multiple Sclerosis Study Group (1993); MSCRG = Jacobs *et al* (1996); PRISMS = PRISMS Study Group (1998). Adapted from Filippini *et al* (2003a). © 2003, with permission from Elsevier.

starting treatment (2.3%: defined as raised thyroid stimulating hormone without abnormalities of serum thyroxine or triiodothyronine) or the development of thyroid-specific antibodies following treatment (23%) were the only predictive factors for the development of thyroid disease. There was no difference in frequency depending on exposure to IFN-β1a or IFN-β1b. There are isolated reports of treatment-related myasthenia gravis (Blake and Murphy 1997), systemic lupus erythematosus (Watts 2000), rheumatoid arthritis (Alsalameh *et al* 1998; Jabaily and Thompson 1997), inflammatory arthritis (Altintas *et al* 2002; Levesque 1999; Russo *et al* 2000), urticaria (D.L. Brown *et al* 2001), Raynaud's phenomena (Cruz *et al* 2000; Linden 1998b), worsening of psoriasis (Kowalzick 1997; Webster *et al* 1996), acute hepatitis (Christopher *et al* 2005) liver failure (E.M. Yoshida *et al* 2001), a fatal capillary leak syndrome (in a patient with pre-existing acquired C1 inhibitor

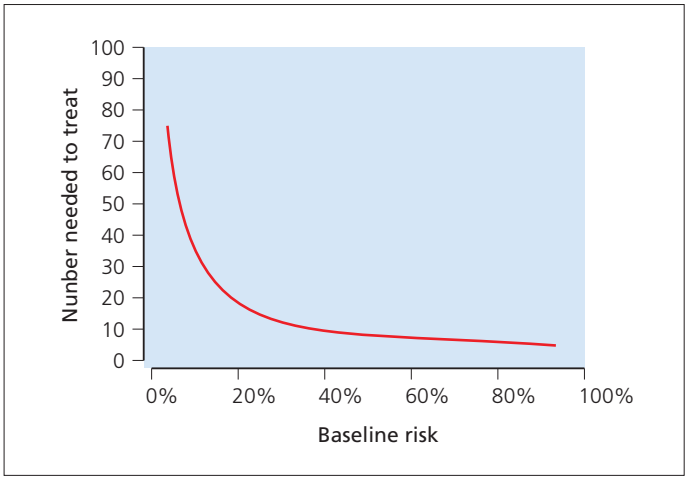


Figure 18.34 Number needed to prevent one patient having at least one exacerbation at 1 year in relation to baseline risks. Adapted from Filippini *et al* (2003a). © 2003, with permission from Elsevier.

deficiency; Niederwieser 2000; S. Schmidt *et al* 1999), intracerebral hemorrhage (Niederwieser *et* al 2001) and anaphylaxis (Clear 1999; Corona *et al* 1999). From amongst this catalogue, the one clear message is that patients with monoclonal gammopathy should not receive IFN-β as they may be at risk for developing a life-threatening capillary leak syndrome.

Neutralizing antibodies to interferons

It is now revealed that up to 45% of patients on 8 MIU IFN-β1b develop neutralizing activity. In the original series, this usually occurred in the first year (34 of 124) with fewer examples thereafter (7 of 124 in year 2, and only 2 of 124 in year 3; IFNB MS Study Group and the UBC MS/MRI analysis Group 1995). In the trial of IFN-β1a (Avonex; Jacobs *et al* 1996), persistent neutralizing anti-interferon activity was seen in 14% of treated individuals by one year and 23% at two years. This compared with 4% in the placebo group, but the positive tests always disappeared with repeat testing. The tendency for neutralizing antibodies to be present transiently has since been confirmed, an early response but at low titre having predictive value for subsequent reversion to seronegativity (Gneiss *et al* 2004). Subsequent experience confirms the significant antigenicity of IFN-β1b and shows cross-reactivity between neutralizing and binding antibodies to IFN-β1b, IFN-β1a and naturally occurring IFN-β. At first, the clinical significance of neutralizing antibody responses remained uncertain (Kivisäkk *et al* 1997). Antibodies are detected by a cytopathic effect on virus-infected cells. Preliminary enzyme-linked immunosorbent assay screening has since been introduced and the prevalence of antibodies in more recent cohorts of patients treated with IFN-β1a is lower than previously published or that seen with IFN-β1b. For IFN-β1b, the original primary and secondary outcome measures have been re-analysed, stratified for the presence of neutralizing antibodies and different epochs within the initial 3 year period of exposure for comparisons of relapse rate, MRI activity and disability. This has generated much uncertainty (and spin) about whether the drug would be even more effective were it not for antibody development or, conversely, is doomed to short-term efficacy (at best) by immunogenicity.

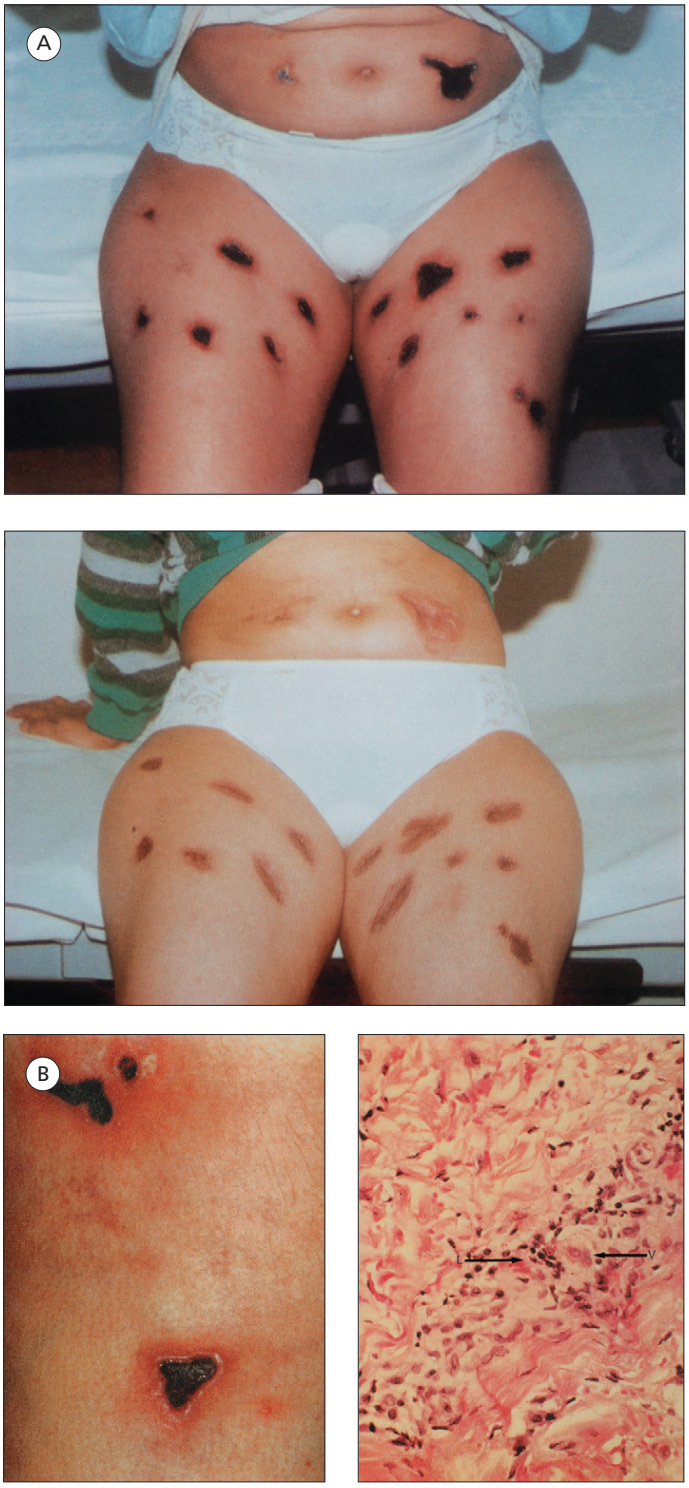


Figure 18.35 (A) Severe necrotizing lesions in a woman with multiple sclerosis undergoing treatment with IFN-β1b at onset (top panel) and on recovery (lower panel). (B) Macroscopic and microscopic appearance of an individual area of necrosis. From Albani and Albani (1997) with permission. © 1997, reproduced with permission of the BMJ Publishing Group.

In support of the first interpretation is the conclusion that patients who do not develop neutralizing activity have an even lower relapse rate than that reported for all IFN-β1b-treated patients. For the period 13–36 months, the attack rate was 1.06 per year in the placebo group compared with 1.08 per year in

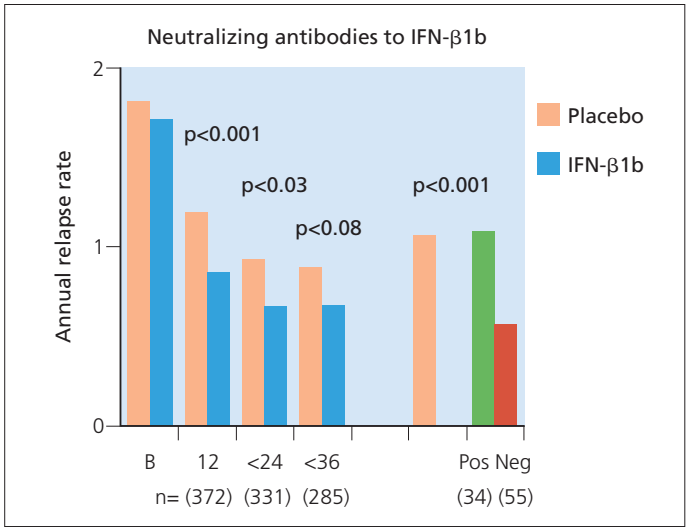


Figure 18.36 Annual relapse rates at baseline (B), and on completion of years 1 (12), 2 (<24) and 3 (<36) in patients taking IFN-β1b; the annual relapse rate is also shown in a subgroup of patients with (Pos) and without (Neg) neutralizing antibodies compared with a cohort of controls studied for the same period. Adapted from the IFNB Multiple Sclerosis Study Group (1993; 1995). © 1993, 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

the IFN-β1b-treated antibody-positive patients and 0.56 per year in those without neutralizing activity (Figure 18.36: IFNB MS Study Group and the UBC MS/MRI Analysis Group 1995). It follows that, at least in this series, the development of neutralizing activity is associated with a relapse rate which is greater than that reported for other treated patients. In fact, patients destined to develop neutralizing antibodies showed a higher relapse rate before neutralizing activity was detected. This increased further after the assay became persistently positive. For this reason, it has been proposed that patients who develop neutralizing antibodies may have a different profile of immune responsiveness which promotes both neutralizing activity and the disease process, culminating in the symptoms of multiple sclerosis. This formulation seems to us contrived.

In the early analyses of these trials, patients who developed neutralizing activity did not become more disabled than the remaining participants. In fact, the converse was true. This was seen as evidence that the development of neutralizing activity does not disadvantage patients in the longer term. However, taken with the increased relapse rate associated with neutralizing activity, this observation merely reflects the poor correlation between relapse and disability, and suggests that inactivity of IFN-β1b *in vivo* does not adversely affect the course of the disease – a conclusion prompting the response that IFN-β1b is therefore not a disease-modifying drug. The effects on MRI activity and total lesion load in patients developing antibodies parallel the observations relating to relapse rates.

To clarify these emerging issues, investigators using IFN-β1b in the pivotal study subsequently published a detailed report on the development of neutralizing antibodies (IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group 1996). They validated the cytopathic assay and confirmed that the original antibody results were not false-positives; although with a change in cut-off point for a positive titration result the prevalence dropped to 35%. Antibodies mainly, but not exclusively, developed in the first year and this complication was not dose dependent. Relapse rates differed depending on the presence of antibodies, as originally reported (IFNB Multiple Sclerosis Study Group 1995). There was more disease activity on MRI in patients who developed antibodies on high (but not low) dose IFN-β1b than the antibody-negative group, but the cumulative number of enlarging lesions was still less than in the placebo group. There was no detrimental effect on disability progression and antibody-positive patients had less disability progression than those patients who remained antibody negative. No new adverse events correlated with the development of neutralizing activity. In fact, beyond 18 months, fewer events occurred than previously reported in studies using IFN-β1b. Individuals who developed antibodies were no more or less likely than others on active treatment to discontinue IFN-β1b.

In the trial of IFN-β1a (Rebif; PRISMS 1998), all the adverse effects were as reported for other brands of IFN-β but they were no more prevalent. Specifically, neutralizing antibodies to IFN-β1a developed in 18% of treated patients and 1% of controls. Although initially reassuring, the extension study (PRISMS-4) did show a detrimental effect on relapse rate in antibody-positive patients (44 μg group, antibody-negative relapse rate was 0.50 per year compared with 0.81 per year in antibody-positive patients). The formation of neutralizing antibodies reduced the protective effect on relapse recurrence in the European trial of secondary progressive multiple sclerosis but did not influence disability progression (Polman *et al* 2003). Neutralizing antibody formation was shown to inhibit the MRI benefit from treatment in the SPECTRIMS trial (SPECTRIMS Study Group 2001).

The neutralizing antibody story has continued to unfold. Although there is still no definitive study of adequate size and duration to provide a final statement on this complex issue, the suspicion that antibody formation reduces both the biologic effect of IFN-β and the clinical and MRI evidence for efficacy have since increased. In a study of 754 Danish patients, Ross *et al* (2000) found that neutralizing antibodies are more common in patients receiving IFN-β1b than IFN-β1a; in patients treated with subcutaneous compared with intramuscular injections, and in those receiving three times weekly injections; compared to once weekly administration. Bertolotto *et al* (2002) found similar results based on a cytopathic effect assay in a study of 125 patients. They reported that those receiving IFN-β1a (Rebif) three times weekly developed neutralizing antibodies with a frequency between that reported for the other preparations (18 month results for persistently positive: IFN-β1b, 31%; subcutaneous IFN-β1a three times weekly, 15%; and intramuscular IFN-β1a once weekly, 2%). Also reviewing the nationwide Danish prescribing experience, P.S. Sorenson *et al* (2003) reported similar findings in 541 IFN-β-treated patients followed for up to 5 years. Using three techniques of varying sensitivity (the findings were similar regardless of the assays used), they found that approximately one-third of IFN-β-treated patients developed neutralizing antibodies in the first year of treatment. This percentage stayed largely unchanged with prolonged follow-up. However, there was considerable variability between the different preparations. Factors leading to a greater risk of neutralizing

antibody formation included exposure to IFN-β1b (compared with IFN-β1a), subcutaneous injection (compared with intramuscular; $p = 0.022$) and repeated dosing (three times weekly compared with once weekly; $p = 0.0001$). Antibody levels fell in the third year in some patients ($p = 0.023$), particularly those receiving IFN-β1b. The presence of neutralizing antibodies influenced the observed relapse rates in this study. Relapse rates were greatest during antibody-positive epochs (0.64–0.70 vs. 0.43–0.46; $p < 0.03$). They confirmed that antibody-positive patients relapse more often than those without antibodies (odds ratio during antibody positive periods: 1.51–1.58; $p < 0.03$) although this loss of protection is usually delayed. MRI data were not reported. These authors speculate that the reduction in prevalence of antibodies with time, and the associated fall in relapse rate may relate, in part, to changing avidity of the antibodies. Bellomi *et al* (2003) reported that the type of IFN-β exposure does not determine whether antibodies are lost with time.

The Danish series found no effect of antibody formation on disability progression as measured by the EDSS (P.S. Sorenson *et al* 2003). Approximately 50% of patients had deteriorated by 1.0 EDSS point (confirmed at 6 months) at the 42 month follow-up. Survival curves, stratified for the presence of neutralizing antibodies, seemed to separate thereafter, suggesting that antibody-negative patients accumulated disability more slowly after the 3 year follow-up, but the number of patients available for follow-up fell sharply after 3 years and this difference was not significant ($p = 0.14$). Taken together, the Danish investigators conclude that the development of antibodies does compromise the effect of IFN-β. They recommend that antibody status should be monitored in patients with active disease and suggest changing to another class of treatment (such as glatiramer acetate or mitoxantrone) in antibody-positive patients.

Oger *et al* (1997) reported that antibody formation correlated with high levels of immunoglobulin production in an *in vitro* immunoglobulin G secretion assay but others (Bellomi *et al* 2003; Rudick *et al* 1998a) were unable to identify markers that predict the development of antibodies. Lawrence *et al* (2003) developed a rapid, inexpensive radio-immunoprecipitation assay to measure binding antibodies to IFN-β. Using a cohort of 33 patients with relapsing–remitting multiple sclerosis, they reported that the assay is predictive both for the presence of neutralizing antibodies and reduced efficacy in preventing MRI outcomes. Gilli *et al* (2003) reported that neutralizing antibodies reverse the putative protective influence of IFN-β on reduction of matrix metalloproteinase-2 and -9 expression but do not influence endogenous levels of the tissue inhibitor (TIMP-1).

In a recent report, Petkau *et al* (2004) analysed the neutralizing antibody data collected during the pivotal North American IFN-β1b trial. They determined that neutralizing antibodies reduce the clinical benefit (relapse reduction) from both doses of IFN-β1b but the detrimental effect of these antibodies is more marked in those receiving the low dose (that is, relapse rates were higher by 28% for 1.6 MIU compared with 2% for 8 MIU: Figure 18.37A and B). They also reported that this reduction in efficacy reverses with restorations of antibody-negative status (60% who were once antibody-positive later had at least one antibody-negative value). Gilli *et al* (2003) reported that neutralizing antibodies developing during the course of treatment with each of the available interferons abrogated the effect of IFN-β on reducing matrix metalloproteinase-9 expression, suggesting a possible mechanism of action for these antibodies.

Against this background, the transactions of a conference devoted to antibody formation in multiple sclerosis have since appeared (Pachner 2003). Attendees reached consensus (>70% agreement) on many of the conclusions already discussed relating to antibody-mediated decrease in bioactivity. They called for more universal standards in the assays used to measure binding and neutralization, longitudinal data analyses to avoid the limitations of previously reported cross-sectional studies (Petkau 2003), and prospective efforts to identify strategies for reducing

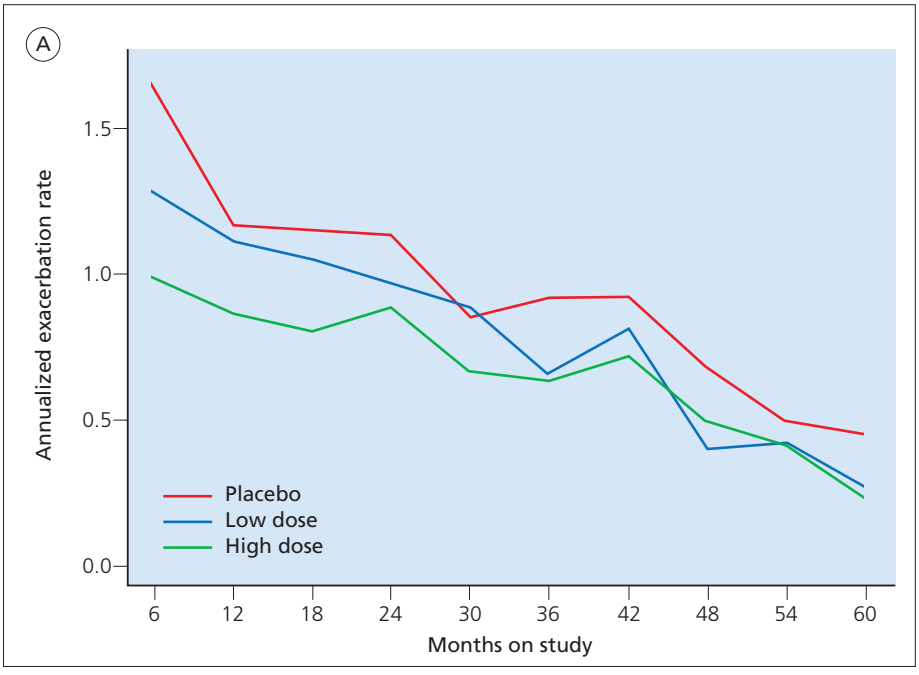


Figure 18.37 (A) Annualized exacerbation rates in the preceding 6 month periods (number of exacerbations beginning in preceding 6 month period/number of patient years on study in preceding 6 month period). Adapted from Petkau *et al* (2004). © 2004, reproduced with permission of Hodder Education.

illustration continued on following page

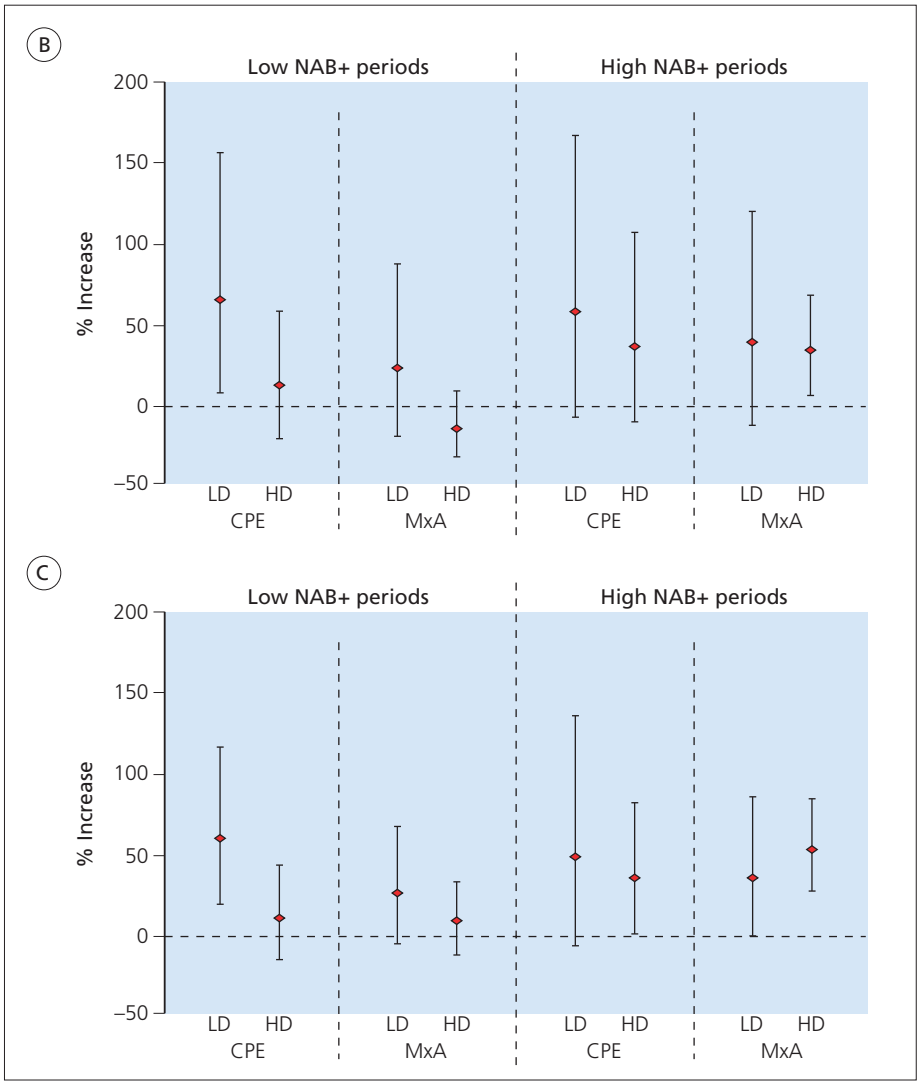


Figure 18.37, cont'd (B and C) Increase in exacerbation rate (and 95% CI) for eventually neutralizing antibody (NAB)+ subgroups in low NAB+ (confirmation required) and high NAB+ (no confirmation required) periods relative to NAB– periods: (B) 'Once positive, always positive' classification of NAB status. (C) 'All switches considered' classification of NAB status. LD = low dose; HD = high dose; CPE = cytopathic effect; MxA = myxovirus protein A. Adapted from Petkau *et al* (2004). © 2004, reproduced with permission of Hodder Education.

antibody formation in patients treated with IFN-β. Strategies for inhibiting the formation of antibodies so as to maintain the perceived efficacy of IFN-β1b include using higher doses, concurrent use of corticosteroids or other immunosuppressants, and switching brands – although the prevailing view is that antibodies to IFN-β1a and IFN-β1b cross-react. In 2005, there are still no proven strategies for reducing antibody formation. The interested reader is referred to a series of recent papers comprising the proceedings of an international consensus conference held in August 2002 (Bertolotto *et al* 2004; Billiau *et al* 2004; Deisenhammer *et al* 2004; Hartung and Munschauer 2004; Hartung *et al* 2004; Schellekens and Casadevall *et al* 2004; Vartanian *et al* 2004).

Malucchi *et al* (2004) recently reported on their non-randomized study of 78 patients treated with either subcutaneous IFN-β1b (Betaseron; n = 20), subcutaneous IFN-β1a (Rebif; n = 25) or IFN-β1b by intramuscular injection (Avonex; n = 33). Neutralizing antibody assays were performed every 3 months for up to 3 years. Their frequency was similar to previous reports in the literature (subcutaneous IFN-β1b, 35%; subcutaneous IFN-β1a, 20%; and intramuscular IFN-β1a, 3%). Relapses were most consistently reduced in the patients without antibodies; patients 'persistently positive' demonstrated less relapse suppression and a greater likelihood of EDSS worsening during the course of the study. In another recent report, Frank *et al* (2004) reported that subcutaneous IFN-β1b reduced the number of contrast enhancing lesions and the cumulative white matter lesion load over a period of up to 3 years in 30 patients using a baseline versus treatment crossover design. The MRI effect was reduced in antibody-positive patients. The authors suggested that IFN-β1b by subcutaneous injection reduced the progression of cerebral atrophy but, from our review of this paper, the benefit is less certain given the small sample size.

Thus, the issue of whether neutralizing antibodies matter is not settled. On one side of the debate is the theory that IFN-β is biologically inactive in the presence of neutralizing antibodies and so should not be prescribed. Antibodies very clearly reduce biological activity and seemingly reverse any effect on frequency of relapse, reducing antibody-positive patients to nearly the same risk of relapse as untreated controls. Several recent studies support the concept that neutralizing antibodies decrease the therapeutic effects of the IFN-βs (G.S. Francis *et al* 2005;

Giovannoni and Goodman 2005; Kappos *et al* 2005; P.S. Sorensen *et al* 2005). The observation that disability continues regardless of antibody formation suggests that this group of drugs provides little in the way of long-term disease modification. Others present these findings and their implications for efficacy and safety in the best possible light; they argue that the development of neutralizing activity has led to the true efficacy of IFN-β1b being underestimated; that neutralizing activity is not associated with additional adverse effects; and that, at worst, it may only make the drug harmlessly inactive.

The licences for IFN-β

By 1996, approximately 35 000 patients in the United States were receiving Betaseron for ambulant, relapsing–remitting disease. The number of patients attending some centres who received a prescription was estimated at >50%. Presumably, there was some laxity in the policing of reimbursements by the insurance companies with a good deal of drift at the prescribing margins. The unofficial guidelines, drafted by neurologists involved in the clinical trials and with postmarketing experience, were orientated towards expanding the group eligible for a prescription and offered advice on managing difficulties which might arise, such as perceived lack of efficacy, without discontinuing treatment (Lublin *et al* 1996). In the first few months after a licence was granted for Avonex, the company claimed 15 000 prescriptions, with a proportion switching from IFN-β1b to IFN-β1a (Avonex), creating considerable confusion with respect to the carryover of clinical benefits, adverse effects and neutralizing antibodies. Because the clinical trials were published later and the granting of a licence was delayed, Rebif lagged in the United States market. In 2003, the approximate number of patients receiving these treatments in the United States (total 172 000 prescriptions) and Europe (94 000 prescriptions) respectively were: Avonex – 47% and 15% (94 500 total); Betaseron – 17% and 38% (65 500 total); Rebif – 10% and 31% (46 500 total); and Copaxone (see below) – 26% and 15% (59 500 total).

It did not take long for a debate to begin on the managed entry of the interferons in continental Europe and the United Kingdom, with jockeying for position on who should take the decision to prescribe and who pays (Walley and Barton 1995). In Europe, where Betaferon was granted a product licence in late 1995, Avonex in 1997 and Rebif in 1998, the professional analysis was much more measured than in the United States. The take-up of prescriptions was slower and in many countries this resulted from delay in establishing guidelines for clinical use, closely linked to decisions on funding. All forms of IFN-β and glatiramer acetate are currently provided in the United Kingdom through a Risk Sharing Scheme, organized by the Department of Health, in which patients on treatment will undergo annual EDSS evaluations for up to 10 years. From these long-term data, the price of the drug may in future be adjusted to meet an acceptable level of cost-effectiveness. Meanwhile, pressure from the neurological community and the commercial realization that the arguments with respect to efficacy and cost are not yet won has led to new trials, some already completed (see above). However, comparative studies with other immunosuppressive drugs, which the prescribing community would want to have available – such as the proposed ERAZMUS (EEC concerted action) trial comparing IFN-β1a (Avonex) with azathioprine and placebo in 1200 patients with early relapsing–remitting or secondary progressive multiple sclerosis, taking time to EDSS 3 over 4 years as the primary outcome measure, are commercially unattractive and have never materialized.

Information distributed by the pharmaceutical companies which make or market Betaseron in the United States recommends that

> *Betaseron™ (interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.*

In the European Community, Betaferon is currently indicated [European Agency for the Evaluation of Medicinal Products (EMEA) European Public Assessment Report (EPAR), Revision 5, 12 June 2003]

> *for the treatment of patients with relapsing-remitting multiple sclerosis and two or more relapses in the last two years. Betaferon is also indicated for patients with secondary progressive with active disease evidenced by relapses.*

In North America, Avonex

> *is indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. Safety and efficiacy in patients with chronic progressive multiple sclerosis have not been established.*

Caution is advised in using Avonex in patients with a history of depression and in those with a prior history of epilepsy. Breastfeeding and Avonex-use should not be combined. In the European Community: Avonex is currently indicated (EMEA EPAR, revision 4, 24 February 2004)

> *for ambulatory patients with relapsing multiple sclerosis characterized by at least two recurrent attacks of neurologic dysfunction (relapses) over the preceding three year period without evidence of continuing progression between relapses. It slows the progression of disability and decreases the frequency of relapses over a two year period. Contra-indications are known hypersensitivity to IFN-β or human albumin, pregnancy, breast feeding, severe depression or suicidal ideation, and poorly controlled epilepsy.*

Avonex is also indicated for the treatment of patients who have experienced a single demyelinating event with an active inflammatory process if it is severe enough to warrant treatment with intravenous corticosteroids; if alternative diagnoses have been excluded; and if they are determined to be at high risk of developing clinically definite multiple sclerosis. The EMEA goes on to suggest that

a high risk patient is one who has ≥ 9 T2 lesions on a baseline MRI and at least one new T2 or gadolinium enhancing lesion on a follow up scan performed at least 3 months later. Treatment should be discontinued in patients who develop disease progression

In the United States

Rebif™ (interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of Rebif™ in chronic progressive multiple sclerosis has not been established.

In the European Community, Rebif is currently indicated (EMEA EPAR, revision 6, 4 December 2003)

for the treatment of patients with multiple sclerosis with two or more relapses within the last two years. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity.

This licence is now updated to recommend 44 μg as the preferred dose.

In the climate which has emerged following the marketing of IFN-β, working in health care systems with competitive and limited resources, such as the United Kingdom, maintaining a balanced and responsible position, remains intermittently stressful but still of importance. Well-tried mechanisms for challenging decisions on prescribing, where medical and fiscal motives are easily confused, have already been exercised. It is somewhat ironic and, for some, frankly perplexing, that the introduction of a treatment that might have a disease-modifying effect in multiple sclerosis should have provoked so much apparent controversy. On one side of this debate are professional and lay enthusiasts who argue that this is the first useful drug treatment for a frightening and potentially disabling neurological disease affecting young adults. On the other, are those who have experienced previous short-lived therapeutic claims and, therefore, remain sceptical about the newly licensed therapies having more than a transitional role on the way to more effective remedies.

In the United Kingdom, all three interferon preparations are currently used according to the guidelines of the Association of British Neurologists (January 2001, see *www.theabn.org*) which require that there have been two or more clinically significant relapses in the previous 2 years in ambulant patients with relapsing–remitting multiple sclerosis and two disabling relapses as the main clinical feature of disease activity in ambulant patients with secondary progressive disease. The guidelines also suggest the following be considered as potential stopping criteria:

- the occurrence of two severe relapses within 12 months
- the development of secondary progression for >6 months
- the loss of ability to walk.

These somewhat rigorous stopping guidelines have not always proved feasible to apply in clinical practice (B.D. Dubois *et al* 2003). The EMEA reports provide a variety of recommendations for monitoring patients and deciding when treatment might be continued or discontinued. These reflect the uncertainties that exist concerning the long-term effectiveness of all the interferons and the frequent difficulties in determining for individual patients whether or not treatment is providing benefit. The use of IFN-β is contraindicated in young people aged <16 years, although the experience of treating a group of Italian children or adolescents is that the reduction in relapse rate is no less than in adults (Ghezzi *et al* 2005). The pivotal trials were usually confined to the 16–55 year age groups, and no upper age limit is included in the summary of product characteristics.

There is a critical need for thorough and transparent analysis of all the prescribing experience with each of these partially effective drugs to characterize, if possible, what determines 'responder' vs. 'nonresponder' status. To date, these analyses have not been possible as the informative clinical trial data are largely unavailable to investigators, being held *in camera* by the sponsors. Given the importance for all parties of identifying clinical and biological markers of response, both to predict who will respond and to clarify the magnitude and duration of a positive response, none of the approved drugs has yet been subjected to such comprehensive analysis. Indeed, investigators have yet to create clinical and MRI guidelines that are either consensus driven or, preferably, biologically meaningful. It remains uncertain whether the 'partial response' so universally reported in contemporary trials relates to a partial response for many or a biologically meaningful response for only a minority of patients. Consequently, patients and their physicians are left to speculate as to when drugs should be started, changed or stopped. This ambiguity has prompted some experts to suggest that since one cannot predict who may respond, virtually all affected individuals should be considered for treatment at the time relapsing–remitting multiple sclerosis is diagnosed (Van den Noort 1998). However, disbelievers amongst the prescribing community argue that the drugs are sufficiently limited in effectiveness as to make their use purely optional and determined more by the desire of the patient and physician to 'do something' rather than realistic expectation of a brighter neurological future.

MOLECULES THAT INHIBIT T-CELL–PEPTIDE BINDING

The principle that immune responses can be manipulated by the use of peptides or other molecules that mimic closely the naturally occurring ligand for T-cell binding has shown that it is possible to promote clonal anergy. These strategies have therefore been applied to the treatment of multiple sclerosis.

Oral myelin

One approach that has already received preliminary clinical application (Weiner *et al* 1993b) is inhibition of the autoimmune processes with oral antigen. Thirty patients, having two or more relapses in the previous 2 years, were treated with 30 mg of oral bovine myelin or placebo for 1 year. Six of the 15 myelin-treated patients had major attacks compared with 12 of the 15 placebo patients. There was no effect on disability, although a rather contrived subgroup analysis claimed a selective effect in DR2(15)-negative males. The clinical observations could not be

correlated with changes in the proportion or specificity of T-cell clones reactive to myelin basic protein, or its encephalitogenic peptides. In other contexts, oral feeding of antigen has been shown to favour the induction of T cells which secrete IL-4, TGF-β and IL-10 at low doses and to delete both Th1 and Th2 cells at higher doses (Y. Chen *et al* 1995). Although superficially attractive, the results of the pilot study always seemed to us overstated and few were surprised by the widely publicized news that the phase three trial of oral myelin (515 patients, 14 sites) showed no clinical effect. However, this negative study remains unpublished several years after the trial was stopped and seems destined never to be reported in full.

Altered peptide ligands

Antigen-specific immunotherapy was dealt a further tough blow in 2000 when two phase two trials of altered peptide ligand therapy designed to interfere with T-cell responses were terminated early because of concerns about patient safety. In the first, use of the altered peptide ligand (CGP77116) was associated with clinical relapses and systemic hypersensitivity reactions that persisted despite dose reduction (Bielekova *et al* 2000). The trial was terminated after only eight patients were enrolled. The finding that two-thirds of patients who had clinical relapses after starting therapy were shown to have developed high T-cell precursor frequencies to the ligand and myelin basic protein peptide 83–89 suggested that the intervention incited clinical relapses. In the second study, three doses of the altered peptide ligand NBI5788 (5, 20 or 50 mg weekly by subcutaneous injection) were compared with placebo administration. The trial was stopped when nine of the 142 patients experienced hypersensitivity reactions. Immunological studies suggested that treatment induced a Th2 profile of immune response (Kappos *et al* 2000). This study was of insufficient duration to detect a clinically meaningful response but MRI monitoring suggested a possible benefit using the lowest dose of altered peptide ligand. D.E. Goodkin *et al* (2000) demonstrated that various doses of a complex of HLA-specific DR2 solubilized with the myelin basic protein peptide 84–102 (AG284) were well tolerated but the trial was not powered for an efficacy analysis.

Copolymer-1 or glatiramer acetate (Copaxone)

Following the logic that immunological damage in multiple sclerosis is mediated by antigen-specific T cells, a synthetic peptide composed of L-alanine, L-glutamic acid, L-lysine and L-tyrosine was designed specifically to mimic the structure of myelin basic protein. Copolymer 1 [Cop-1, later renamed glatiramer acetate (Copaxone) by the sponsor upon approval of this agent for use in multiple sclerosis by the FDA in North America] was neither encephalitogenic nor toxic, and was shown to suppress experimental autoimmune encephalomyelitis (perhaps by inducing antigen-specific suppressor cells). It moved into clinical practice in the early 1980s (Abramsky *et al* 1977).

Clinical studies

Bornstein *et al* (1982) first reported in detail on the therapeutic use in 16 patients with multiple sclerosis. In a subsequent blinded and placebo-controlled study of patients having two or more relapses in the previous 2 years, and EDSS scores of <6 at entry, randomization to active or placebo preparations was within EDSS bands (Bornstein *et al* 1987). Participants received subcutaneous Cop-1 for up to 2 years. A neurologist assessed disease activity, and analysis was on an intention to treat basis. Taking absence of relapse during the trial as the primary end point, a greater proportion of individuals in matched pairs randomized to Cop-1 were relapse free on completion than placebo cases (ten of 22 compared with two of 22 in whom the placebo partner but not the Cop-1-treated individual was free from relapse, and ten of 22 pairs in whom the course was concordant within individual pairs; $p = 0.039$: Figure 18.38A). There were 62 exacerbations in 23 placebo-treated patients compared with 16 amongst 25 Cop-1-treated individuals. Although the placebo group showed a reduction in relapse rate during the trial as part of the natural history, or regression to the mean, the difference between groups was 4.9 in the first year and 3.3 in the second, favouring treatment with Cop-1. Overall 14 of 25 treated patients were free from relapse compared with six of 23 in the placebo group ($p < 0.001$). An apparent difference in the rate at which Cop-1- and placebo-treated patients deteriorated (five of 25 and 11 of 23, respectively), which was especially marked in less affected individuals (EDSS <2 at entry), was not statistically significant. There was, however, a delay in time to progression by one EDSS point amongst Cop-1-treated patients (Figure 18.38B). Local injection site reactions seriously undermined blinding in this study and 29 of 40 participants (in whom information was available) correctly guessed treatment assignments (the authors suggest that unblinding was also influenced by the response to treatment). Subsequently, Bornstein *et al* (1991) completed a study of 106 patients with secondary progressive multiple sclerosis who had documented evidence for an increase in disability over the preceding 6–18 months. Treatment had no effect on the proportion of patients showing sustained progression by a further one EDSS point. Apart from local skin reactions at the injection site, Cop-1 was well tolerated.

The result of the above study was presumably influential in the decision to design a phase three trial involving patients with relapsing–remitting multiple sclerosis and using relapse rate as the primary outcome. This involved 251 patients randomized to Cop-1 (20 mg by daily subcutaneous injection for 2 years; $n = 125$) or placebo ($n = 126$; K.P. Johnson *et al* 1995). The relapse rate over 2 years in treated patients was 1.2 ± 0.1 compared with 1.7 ± 0.1 in controls (a 29% reduction giving annual rates of 0.6 and 0.8, respectively; $p < 0.007$: Figure 18.39A). More Cop-1-treated patients were free from relapse, and treatment also favoured a delay in time to relapse. With respect to disability, the proportions of patients taking Cop-1 who were unchanged, improved or worse by 1 EDSS point were 54%, 25% and 21% compared with 56%, 15% and 29%, respectively, in the placebo group (Figure 18.39B). Results of the pivotal North American trial led the FDA to approve Cop-1 for the reduction of exacerbations in patients with relapsing–remitting multiple sclerosis. (As noted above, following FDA approval for licensure the company renamed the agent glatiramer acetate or Copaxone.) A United Kingdom licence for the same indication followed in 2000 and in the rest of the European Union in 2001 (*www.tevapharm/com/copaxone/*). In the United Kingdom, the

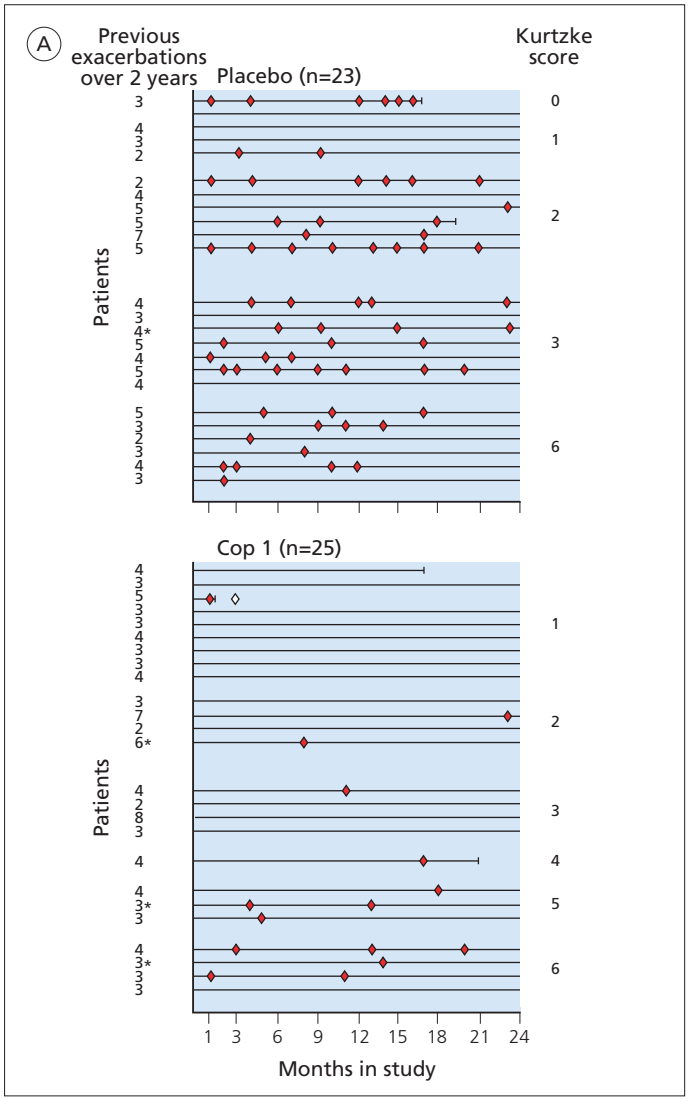


Figure 18.38 Treatment of multiple sclerosis with copolymer-1. (A) Exacerbations occurring during the 2 years of the trial; each line represents a patient and each diamond represents an exacerbation. Patients are grouped according to their EDSS on entry. The number of pretrial exacerbations is indicated to the left. Discontinuous lines represent patients who withdrew before completion. The open diamond indicates an exacerbation occurring after withdrawal which was included as a study event. Patients who were not included in the matched-pair analyses are indicated by an asterisk. (B) Survival curves representing the probability of no worsening from the baseline EDSS; worsening was determined when first observed but was counted only if it continued for 3 months. Adapted from Bornstein *et al* (1987). © 1987, reproduced with permission of the Massachusetts Medical Society.

Association of British Neurologists guidelines on eligibility criteria for glatiramer acetate are:

- ambulant patients with relapsing–remitting multiple sclerosis able to walk at least 100 m without support (EDSS ≤5.5)
- at least two clinically significant relapses in the last 2 years
- age ≥ 18 years.

The pivotal North American glatiramer acetate (or Copaxone, see above) study has been continued. In a blinded extension for up to 11 additional months, there was no loss of effect on relapse rate. Sustained disability was seen in 23% of patients receiving glatiramer acetate compared to 29% of controls (K.P. Johnson *et al* 1998). The European–Canadian glatiramer acetate MRI study was designed to evaluate the effect of treatment on MRI features of disease activity in relapsing–remitting multiple sclerosis (Comi *et al* 2001b). Two hundred and thirty-nine patients with relapsing–remitting multiple sclerosis from 29 centres in seven countries were randomized to receive daily subcutaneous injections of placebo or glatiramer acetate (20 mg). Monthly MRI studies were performed for 9 months. This study demonstrated that treatment reduced the total number of gadolinium enhancing lesions (overall reduction, 29%; $p = 0.003$: Figure 18.40) although a large number of enhancing lesions were still seen in treated patients. This effect was first apparent after approximately 6 months of treatment (Figure 18.41). There was no difference, however, in the proportion of patients showing MRI contrast enhancements (although the specific data were not reported). Notably, only three treated patients remained free of contrast enhancing lesions during the 9 month study. T_2 volume continued to worsen in both groups but to a lesser degree in those receiving glatiramer acetate. The change in hypodense lesion volume was not significantly different between groups. Treatment also reduced the number of relapses but not for the first 6 months. A subsequent publication from this prospective study reported that treatment with glatiramer acetate reduced the proportion of the 1722 new contrast enhancing MRI lesions that developed into persisting hypodense T_1 'black holes', at 7 months ($p = 0.004$) and 8 months ($p = 0.0002$) after they were first detected in the 239 participants (Filippi *et al* 2001a) but not at the 6 month assessment (Filippi *et al* 2002c; N.D. Richert 2002). These reports suggest

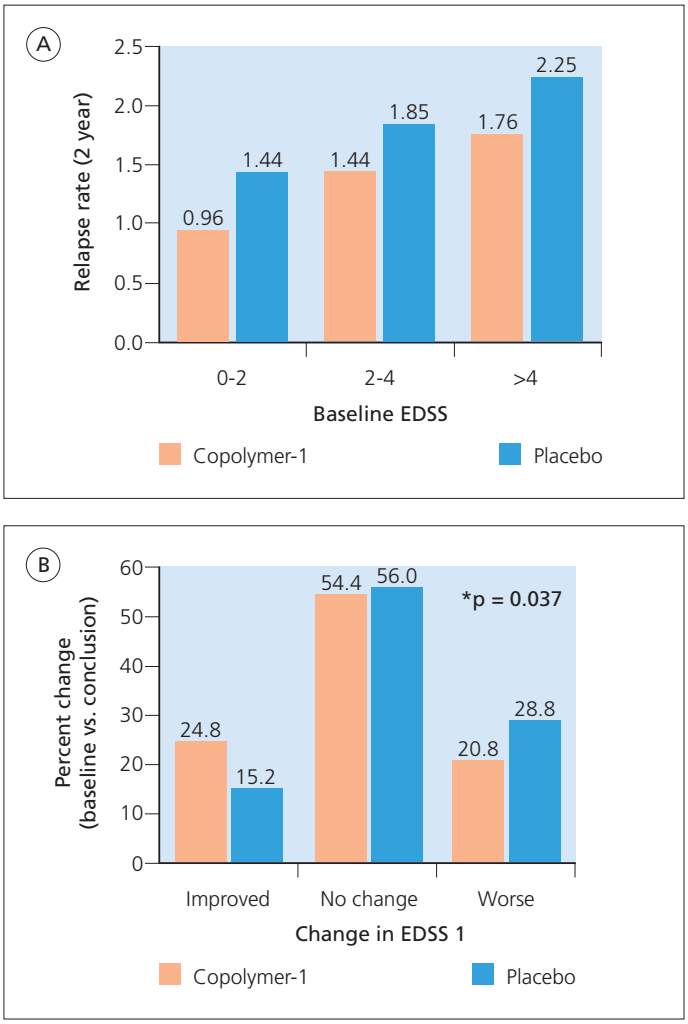


Figure 18.39 Treatment of multiple sclerosis with copolymer-1. (A) Changes in relapse rate observed over 2 years, by baseline EDSS. Numbers above each bar represent the mean 2 year relapse rate for each group. (B) Percentage of patients who improved, were unchanged, or were worse by ≥1 EDSS points between baseline and the last (24 month) measurement (repeated measures ANCOVA). Numbers above each bar represent the percentage of patients in the respective copolymer-1 or placebo group. Adapted from K.P. Johnson *et al* (1995). © 1995, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

that glatiramer acetate has less immediate impact on MRI markers of inflammatory demyelination than IFN-β but may favourably affect the proportion of MRI lesions that develop significant axonal loss.

A 9 month, placebo-controlled trial of glatiramer acetate in 239 pateints with relapsing–remitting multiple sclerosis revealed a mean 0.7–0.8% reduction in central cerebral volume with no significant differences between the patient groups (Rovaris *et al* 2001c). The study showed a weak association between enhancing lesion numbers and atrophy. Rovaris *et al* (2002b) later designed a small, prospective study of glatiramer acetate on the formation of new T_2 lesions and (new and total) contrast-enhancing MRI lesions. This cohort of 20 patients with relapsing–remitting multiple sclerosis underwent monthly MRI studies during both pretreatment and posttreatment periods of observation (two sessions of monthly scans beginning 5 months before and then restarting 90 days after treatment with daily subcutaneous injections of glatiramer acetate, 20 mg). Patients were given both a standard and triple dose of gadolinium separated by 12–24 hours. Using MRI measures of disease activity based on pretreatment behaviour, the authors concluded that treatment reduced both new T_2 and new and total gadolinium enhancing lesion formation. The benefit was detectable within 4 months of starting therapy. In addition, glatiramer acetate reduced the number of contrast enhancing lesions using all doses of contrast enhancing agent. These observations suggested that, in the context of multiple sclerosis, glatiramer acetate may reduce the number of inflammatory lesions in situations of both mild and severe blood–brain barrier disruption – although this conclusion is necessarily based on an indirect measure of blood–brain barrier integrity.

A large, phase III, randomized, double-blinded, placebo-controlled trial designed to determine whether either of two doses of daily oral glatiramer acetate (5 and 50 mg) were superior to placebo in reducing relapse rate (primary outcome), MRI activity (secondary outcome) or disability (tertiary and other end points) was terminated after an interim analysis at 14 months suggested little likelihood of a positive outcome. The results are not yet published.

The clinical relapse rates of 85 patients with relapsing–remitting multiple sclerosis who switched from IFN-β1a (6 MIU by intramuscular injection for 18–24 months) to glatiramer acetate (20 mg by subcutaneous injection daily) either for reasons of perceived lack of efficacy (62 patients) or persistent intolerance to treatment-related side effects (23 patients) were evaluated by O.A. Khan *et al* (2001b). After a further period of 18–24 months prospective follow-up, the authors concluded that glatiramer acetate administration reduces relapse rate in patients previously not fully responsive to IFN-β. The degree of reduction is no less than in patients who responded but switched because of drug intolerance.

Although this result invites the conclusion that glatiramer acetate can rescue patients who fail on treatment with IFN-β, no definitive studies comparing the relative efficacies of these drugs are available although several trials are in progress. A comparison was made by O.A. Khan *et al* (2001c) of clinical outcomes at 18 months in a group of 156 patients with relapsing–remitting multiple sclerosis followed prospectively. In this open label, non-randomized and unblinded study, patients were permitted to choose no treatment (n = 33) or standard doses of intramuscular IFN-β1a (Avonex; n = 40), subcutaneous IFN-β1b (Betaseron; n=41) or glatiramer acetate (n = 42). At 18 months, 122 patients remained in the study (18/34 drop-outs were from the 'no treatment' group). Annual relapse rates were significantly reduced only by glatiramer acetate (0.49; p = 0.001) and subcutaneous IFN-β1b (0.55; p = 0.001) but not by intramuscular IFN-β1a (0.81) compared with the 'no treatment' group (1.02). Similarly, the percentage of relapse-free patients was significant only for glatiramer acetate and subcutaneous IFN-β1b (33% for both; p = 0.05; intramuscular IFN-β1a, 12%; no treatment, 7%). Mean change in EDSS also favoured these two treatment groups (IFN-β1b: –0.25, p = 0.010; glatiramer acetate: –0.44, p = 0.003; IFN-β1a +0.19, p = 0.452 compared with untreated patients: +0.60).

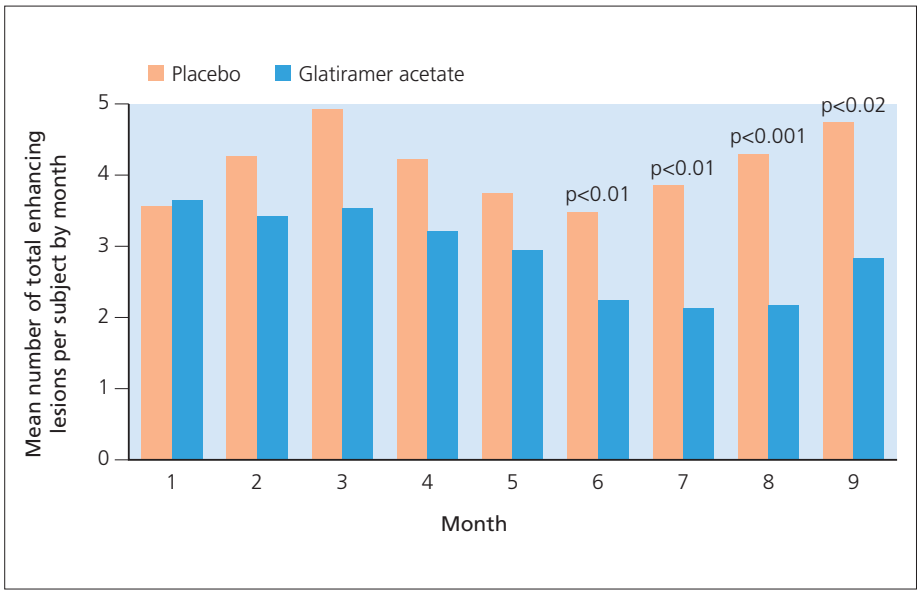


Figure 18.40 European/Canadian trial of glatiramer acetate in relapsing–remitting multiple sclerosis. Median number of total enhancing lesions per subject observed at each month on study using the last observation carried forward. Repeated measures analysis favoured a treatment effect for glatiramer acetate (p = 0.003). Adapted from Comi *et al* (2001b). © 2001, reproduced with permission of John Wiley & Sons.

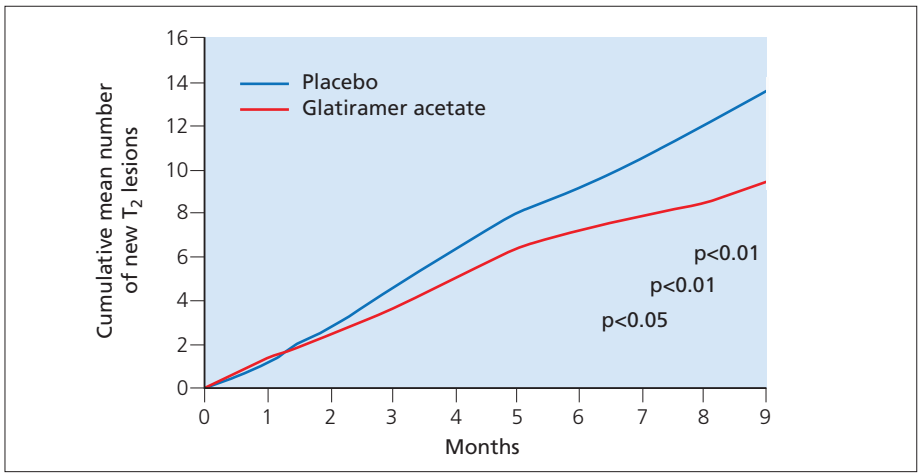


Figure 18.41 European/Canadian trial of glatiramer acetate in relapsing–remitting multiple sclerosis. Cumulative mean number of new lesions observed on the T_2-weighted images at each month on study. Statistically significant differences first emerged after 5 months on treatment. Adapted from Comi *et al* (2001b). © 2001, reproduced with permission of John Wiley & Sons.

The impact of this study is clearly reduced by the design, but nevertheless it provides some evidence that, in practice, glatiramer acetate may have similar efficacy to IFN-β1b, and both are superior to IFN-β1a. A large, National Institutes of Health funded, phase three trial comparing IFN-β1a by once weekly subcutaneous injection (Avonex) and glatiramer acetate (Copaxone) given either alone or in combination (four treatment arms) to patients with relapsing–remitting multiple sclerosis is in progress in the United States (Fred Lublin, personal communication) An open label prospective study of modest size is already reassuring with respect to safety issues (Lublin *et al* 2001; 2002). Clearly, these turf wars are not yet settled.

Munari *et al* (2004; 2004b) completed a systematic review of glatiramer acetate and concluded that there is no conclusive evidence that this agent alters relapse or progression rate in patients with multiple sclerosis. The interested reader is referred to correspondence rebutting and supporting the methodological assumptions that led to this conclusion (Caramanos and Arnold 2005; Comi *et al* 2005; deJong *et al* 2005; Munari and Filippini 2005).

PROMISE was a massive, randomized, double-blind, placebo-controlled phase three study involving 943 primary progressive patients randomized in a 2:1 ratio either to receive glatiramer acetate or placebo. It was recently terminated after an interim analysis suggested futility (Wolinsky *et al* 2004). There were no safety concerns and doubtless post-hoc analyses will add greatly to our understanding of the nuances of testing therapies in this disease category. PROMISE was not fulfilled.

Adverse effects

Glatiramer acetate is generally well tolerated. It is usually possible to initiate treatment at full strength (20 mg by subcutaneous daily injection) without dose titration. Although a daily subcutaneous injection is required, rarely do patients discontinue this drug because of intolerance. In the early reports (Bornstein *et al* 1982; 1987) and pivotal North American trial (K.P. Johnson *et al* 1995; 1998), there is comment on an unpredictable, sometimes frightening but transient and usually self-limiting systemic reaction (facial flushing, chest tightness, anxiety,

palpitations and dyspnoea) lasting for around 30 minutes immediately after an injection. This is experienced by up to 15% of patients (but not recurring in 50%) with an estimated frequency of one episode per 840 injections (K.P. Johnson *et al* 1998). It is important to warn patients but, although alarming, it is seemingly an innocent adverse effect. Approximately two-thirds of patients notice pain at the injection site. Local irritation may occur in 2–3% (K.P. Johnson *et al* 2000) but skin breakdown is very rare (Johnson *et al* 1998). Focal atrophy of subcutaneous tissue at injection sites and adjacent lymphadenopathy may develop (Windhagen *et al* 2001). Glatiramer acetate is not associated with laboratory abnormalities and routine blood studies are not needed to monitor its safety. There are no important drug interactions.

Treated patients may develop antibodies to glatiramer acetate. However, unlike the situation with neutralizing antibodies to IFN-β, experimental and clinical evidence does not suggest that these anti-glatiramer acetate antibodies reduce biological function (Teitelbaum *et al* 2003). This has been shown in assays that measure binding to MHC molecules, T-cell stimulation, interference of competition between glatiramer acetate and myelin basic protein peptide, cytokine production by glatiramer acetate-specific T-cell clones and *in vivo* inhibition of experimental autoimmune encephalomyelitis (Aharoni *et al* 1998; T. Brenner *et al* 2001; C. Farina *et al* 2002; Teitelbaum *et al* 1973; 1991; 2003).

Mechanism of action

As for IFN-β, the precise mechanism(s) whereby glatiramer acetate influences the course of multiple sclerosis continues to be discussed (Dhib-Jalbut 2002; Neuhaus *et al* 2001; Yong 2002). Table 18.8 and Figures 18.42 and 18.43 itemize many of the key findings and provide references to the supporting literature. As discussed earlier, interferon administration is generally followed within weeks by a striking reduction in MRI evidence of blood–brain barrier disruption. This effect is much less dramatic following the administration of glatiramer acetate although MRI activity reduces gradually over a period of several months (see above, Comi *et al* 2001b). This may be explained by the finding that glatiramer acetate does not significantly inhibit T-cell migration (Dufour *et al* 2000; Prat *et al* 1999).

Each drug influences T-cell function (especially CD4 cells) in ways that both overlap and are distinctive. Each agent blocks T-cell activation and promotes Th2 (IL-4, IL-5, IL-10, IL-13 and TGF-β) cytokine production. Unlike IFN-β, however, glatiramer acetate induces the production of regulatory T cells in the periphery. These glatiramer acetate reactive cells cross the blood–brain barrier, respond to central nervous system myelin antigens by secreting Th2 (M. Chen *et al* 2001; Y. Qin *et al* 2000) and Th3 cytokines (Aharoni *et al* 2003) that inhibit Th1 cells, thereby effecting so-called 'bystander suppression'. Glatiramer acetate-reactive cells may also induce anergy (Gran *et al* 2000b).

Recently, abundant evidence has accumulated that glatiramer acetate-specific cells secrete brain-derived growth factors (Aharoni *et al* 2003; Kappos and Duda 2002; Ziemssen *et al* 2002) raising the intriguing possibility that this agent may enhance repair at the site of the multiple sclerosis lesion by inducing a degree of localized 'neuroprotective autoimmunity'.

Table 18.8 Presumed mechanisms of action of glatiramer acetate (adapted from J. Zhang *et al* 2002 with permission)

Modulates T-cell activation and/or proliferation
Competes for binding sites of MHC class II antigens (MBP, PLP, MOG: Ben-Nun *et al* 1996; Fridkis-Hareli *et al* 1994; Fridkis-Hareli and Strominger 1998; Racke *et al* 1992; Teitelbaum *et al* 1996; 2003)
May modify dendritic cell costimulation processes (Hussien *et al* 2001) or act as weak/partial T-cell receptor agonist (Wiesemann *et al* 2001)
Reduces proliferation of MBP-reactive T cells (Duda *et al* 2000; Karandikar *et al* 2002; Neuhaus *et al* 2000)
Actives both Th1 and Th2 cells (Zang *et al* 2003)
Increases ratio of anti-inflammatory (Th2) to proinflammatory (Th1) cytokines
Increases IL-10, IL-4, and IL-6 production (C. Farina *et al* 2001; Hussien *et al* 2001; Neuhaus *et al* 2001a) and decreases IL-12 production (Hussien *et al* 2001)
Increases and then decreases IFN-γ secretion with repeated antigen stimulation (Aharoni *et al* 1997)
Upregulates CD8+ T-cell responses (Karandikar *et al* 2002)
Induce regulatory Th2/3 cells that penetrate the central nervous system and express their anti-inflammatory cytokines and neurotrophic factors *in situ* in animal models of multiple sclerosis (Aharoni *et al* 2003)
Induces TNF-α and IFN-γ production (C. Farina *et al* 2001; Neuhaus *et al* 2000; Zang *et al* 2003)
Enhances production of brain-derived nerve growth factor (Ziemssen *et al* 2002)
Reduces monocyte (Weber *et al* 2004) and antigen-presenting cell function (S. Jung *et al* 2004; H.J. Kim *et al* 2004)

MHC = major histocompatibility complex; IL = interleukin; ; TNF = tumour necrosis factor; MBP = myelin basic protein; PLP = proteolipid protein; MOG = myelin oligodendrocyte glycoprotein; Th = T-helper cell.

The idea that inflammation may enhance remyelination has attracted great interest in the experimental literature (Kipnis *et al* 2000; M. Rodriguez and Lennon 1990; Schori *et al* 2001; Schwartz 2001; Schwartz *et al* 1999; Schwartz and Kipnis 2001) and is discussed more fully in Chapter 10. Recently, M.S. Weber *et al* (2004) have reported that glatiramer acetate blocks monocyte reactivity *in vitro* using cells from treated patients. Both S. Jung *et al* (2004) and H.J. Kim *et al* (2004) have shown that glatiramer acetate also reduces the function of antigen-presenting cells. Together, these studies demonstrate that the mechanisms of action of glatiramer acetate extend well beyond the lymphocyte population of immune cells.

An enzyme-linked immunoadsorbent spot (ELISPOT) assay was developed by C. Farina *et al* (2002) that may correlate 'responder' status to glatiramer acetate. They created three immunological criteria (reduced proliferative response to glatiramer acetate, *in vitro* activation of IFN-γ-producing cells, and activation of IL-4-producing cells) and found that 13 of 15 clinical responders (87%) met two or all three criteria, compared with 22% of patients who appeared to be failing treatment. If correct, this assay may ultimately find more widespread use and lead to the development of other *in vitro* measures to inform treatment decisions.

Antibodies to glatiramer acetate develop within 3 months and may later diminish (T. Brenner *et al* 2001; C. Farina *et al* 2002).

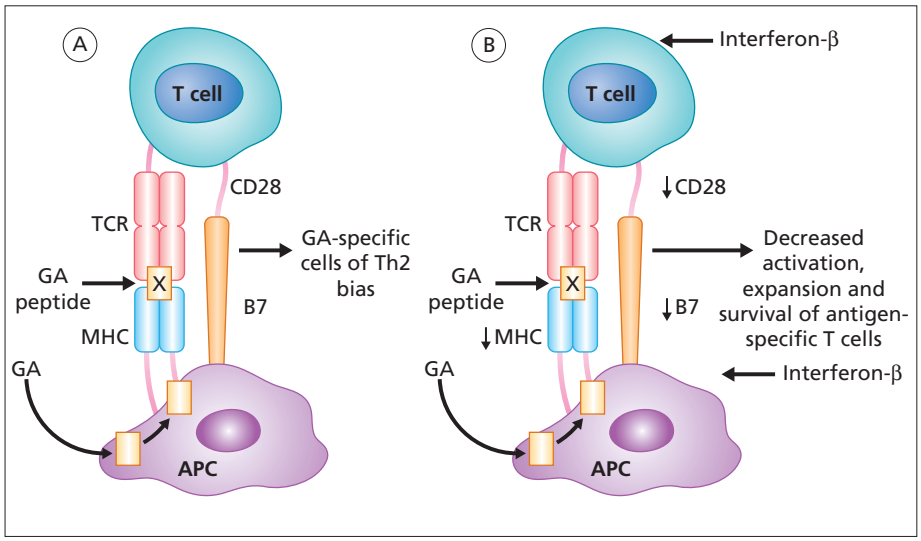


Figure 18.42 Mechanisms of action of glatiramer acetate (GA) and beta-interferons on antigen presentation. (A) The high affinity of GA for the MHC groove or the uptake of GA by an antigen-presenting cell leads to the presentation of GA as an antigen and the generation of GA-specific Th2-biased cells. (B) IFN-β acts on its receptor on T cells and antigen-presenting cells. This decreases the expression of molecules needed for antigen presentation. Together with a further activity of interferon on T-cell expansion and survival, this leads to the decreased generation of antigen-specific T cells. X refers to an antigen-siting in the MHC groove; TCR = T-cell receptor. Adapted from Yong (2002). © 2002, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

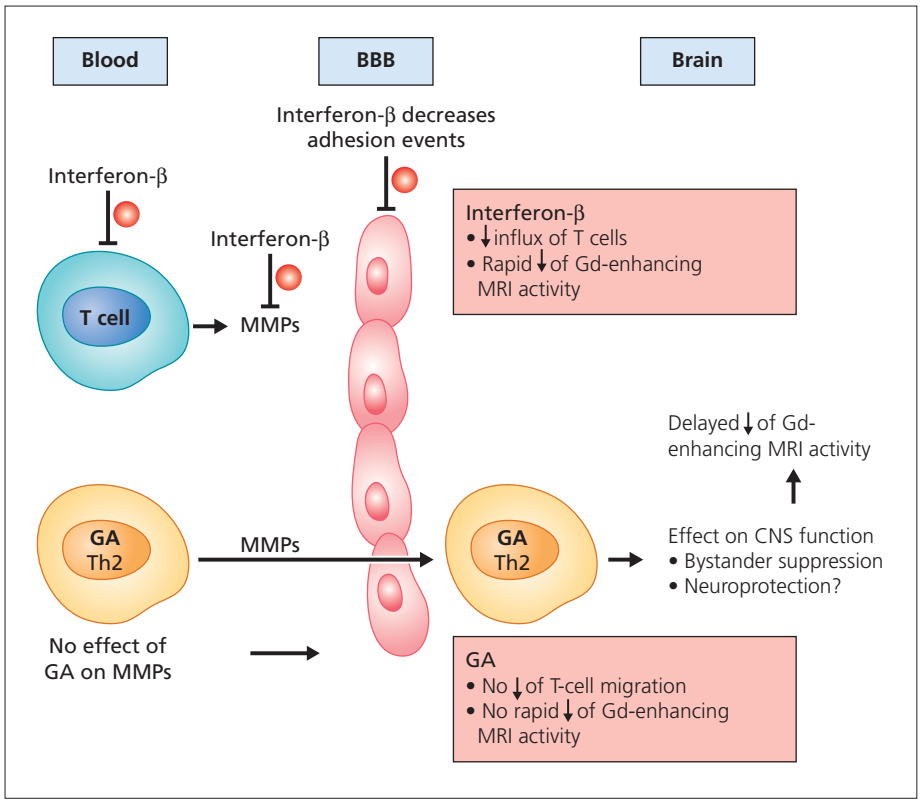


Figure 18.43 Effects of glatiramer acetate (GA) and IFN-β on the blood–brain barrier (BBB) and within the central nervous system. IFN-β reduces the production of matrix metalloproteinases (MMP) by T cells and diminishes the adhesion of T cells to endothelium. These two effects reduce the influx of T cells into the central nervous system. GA-specific Th2 cells traffic into the central nervous system to produce local bystander immune suppression and possibly exert neuroprotection. Gd = gadolinium. Adapted from Yong (2002). © 2002, reproduced with permission of Lippincott Williams & Wilkins (lww.com).

There is great interest in whether these antibodies reduce the clinical benefit of glatiramer acetate (see the discussion of the possible influence of neutralizing antibodies on clinical effects of the interferons). In a large series of *in vitro* and *in vivo* experiments, Teitelbaum *et al* (2003) reported that these antibodies do not seem to reduce activity. A subsequent study, however, reported that antibodies to glatiramer acetate reversed many of these putative activities, including the effect on T-cell proliferation and both pro- and anti-inflammatory cytokines (Salama *et al* 2003). More work is therefore needed to clarify these ambiguities.

Early work of great interest suggests that antibodies to glatiramer acetate induce remyelination in the Theiler's virus animal model of demyelinating disease (Ure and Rodriguez 2002). This finding parallels the observation that immunoglobulins directed against central nervous system antigens also induce abundant remyelination in this animal model (Bieber *et al* 2003; Ciric *et al* 2003; 2004; Mitsunaga *et al* 2002; M. Rodriguez and Lennon 1990) and raises the possibility that anti-glatiramer acetate antibodies may enhance repair of the lesion in multiple sclerosis.

In what ways might these two agents complement their mechanisms of action? Zang *et al* (2003a) showed that, when tested

together *in vitro*, IFN-β1a and glatiramer acetate act to antagonize their respective modes of action. Specifically, IFN-β1a blocked glatiramer acetate-induced T-cell proliferation and the drug-specific pattern of cytokine production was lost. Glatiramer acetate induced both Th1 (TNF-α and IFN-γ) and Th2 (IL-4 and IL-10) cytokines. Conversely, IFN-β inhibited Th1 cytokine production. Together, IFN-β reduced the number of IFN-γ-producing cells compared to glatiramer acetate alone – suggesting another type of antagonism between these two agents. Firm conclusions on the practical and immunological aspects of combination therapy seem premature.

The licence for Copaxone

In the United States, information distributed by the pharmaceutical company that markets glatiramer acetate states that this agent is

> *recommended for reduction of the frequency of relapses in patients with relapsing remitting multiple sclerosis. It is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol and is not recommended for use in pregnancy. The safety and efficacy of glatiramer acetate is unknown in nursing women, in those with impaired renal function, in patients <18 years old, and in the elderly.*

Copaxone was approved for marketing in the United Kingdom and launched in December 2000 with the same general indications. This first approval in a major European market led to extension throughout the European Union by the end of 2001 under the European Mutual Recognition Procedure with the United Kingdom acting as reference member state.

TREATMENTS THAT TARGET T CELLS

In view of the conditional benefits of immune suppression in the treatment of patients with multiple sclerosis, attention has turned to alternative means of interfering with the sequence of events that leads to tissue injury. The theoretical basis for designing therapies, the experimental evidence that they might work, such clinical evidence as there is for efficacy, and the reasons why theory does not always translate into clinical success were admirably reviewed by R. Hohlfeld (1997). These approaches include:

- the use of monoclonal antibodies that achieve much more precise immunological effects than nonspecific immunosuppressants
- reagents which block recognition between antigen-presenting cells and responder lymphocytes
- depletion of autoreactive lymphocyte populations by T-cell vaccination
- bone marrow transplantation.

The validity of these approaches has yet to be confirmed and most are conditional on whether the central hypothesis for the role of T cells in the pathogenesis of inflammatory demyelination is correct. Most of these therapies target circulating white blood cells, in particular lymphocytes, and so qualify as potential disease-modifying treatments in multiple sclerosis. We retain a brief discussion of the earlier studies as background to the current interest in this strategy.

Anti-lymphocyte globulin

The first trial, assessing treatments designed to target circulating lymphocytes and adopting a double-blind and placebo-controlled protocol, was reported in 1982. Inevitably it was underpowered. Forty-three patients with relapsing–remitting multiple sclerosis were randomized to treatment with anti-lymphocyte globulin, azathioprine and prednisolone in combination for 1 month, followed by azathioprine (3 mg/kg) alone for a further 14 months, or placebo preparations. The reduction in relapse rate from 1.0 to 0.7 in the treated group, time to first episode and accumulation of disability all favoured an effect of treatment but the magnitude of these results did not impress the investigators, who reported their findings as offering no more than an indication for continuing to evaluate immunosuppression in the context of multiple sclerosis (Mertin *et al* 1982).

Total lymphoid irradiation

Cook *et al* (1986) first compared total lymphoid irradiation given over 5 weeks with sham irradiation in a group of 45 patients with secondary progressive multiple sclerosis. They reported a beneficial effect on time to further sustained progression, especially over the first 12 months of the study. This clinical response was anticipated by a reduction in absolute lymphocyte count to $<850/mm^3$ and only these patients showed lower functional impairment scores for up to 4 years after the start of treatment. Wiles *et al* (1994) studied 27 patients (the plan was to study 56 but recruitment proved difficult) randomized to active or sham irradiation with 1980 cGy to the lymphoid system and spleen. There was no difference between groups in the clinical course over 2 years, other than a small improvement in bladder function. However, MRI activity was reduced. Three patients died – two, sham-treated, from respiratory complications of multiple sclerosis, and one, who received total lymphoid irradiation, from cardiac failure. Although these fatalities were not related to lymphoid irradiation, the treated group experienced more adverse effects than controls. Subsequently, Cook *et al* (1995) claimed that the concomitant use of corticosteroids further improved the effects of total lymphoid irradiation, and that this additional benefit correlated with the emergence of T cells having the $CD^+/CD3^-$ or $CD8^+/CD3^-$ phenotype. Mortality after total lymphoid irradiation was 1% compared with 14% in the sham-treated group. With EDSS scores at entry of >6.5, these were moderately severely affected patients at the outset.

Monoclonal antibodies

With developments in therapeutic immunology came the opportunity to design small molecules and monoclonal antibodies targeting one component only of the immune system, and leaving the rest intact. In theory, chimaerization and humanization reduce the immunogenicity of therapeutic antibodies and allow courses of reagents having prolonged effects to be given repeatedly (Winter and Milstein 1991). A single pulse of treatment

can induce prolonged alteration in immunological behaviour long after the targeted immune population has been reconstituted (S. Qin *et al* 1993). Anti-CD6 (Hafler *et al* 1986), anti-CD2 (Hafler *et al* 1988), anti-CD3 (Weinshenker *et al* 1991b), anti-CD4 (Lindsey *et al* 1994a; 1994b; van Oosten *et al* 1997; Racadot *et al* 1993) and anti-CD52 (Moreau *et al* 1994; 1996) antibodies have all been administered to patients with multiple sclerosis. In some instances, anti-globulin responses and acute adverse effects limited the usefulness of these potential treatments and an additional problem has been modulation of the targeted lymphocyte antigen, allowing some cells to survive.

Anti-CD6

Using a murine antibody which recognizes the T12 antigen (CD6) present on most (post-thymic) T lymphocytes (but neither chimaeric nor humanized), together with corticosteroids, Hafler *et al* (1986) reported clinical stabilization in six of 12 patients with secondary progressive multiple sclerosis (severe enough to require the recent use of a wheelchair in two cases) at 6 months in an open uncontrolled study. This effect was maintained for a further 3 months in three of these responders. Human anti-mouse antibodies developed within 7 days in seven of nine patients in whom assays were performed. Recovery of circulating T12 cells was rapid and there was evidence *in vitro* for antigen modulation. Studies of cerebrospinal fluid did not suggest that antibody had entered the central nervous system.

Anti-CD3

Weinshenker *et al* (1991c) treated 16 patients, selected for recent rapid accumulation of disability or a high relapse rate, with 50 mg of an anti-CD3 monoclonal antibody (OKT3) over 10 days. Each received corticosteroids and non-steroidal anti-inflammatory drugs. One patient developed anaphylaxis within minutes of receiving the first dose of OKT3 and did not continue in the protocol. A variety of systemic symptoms occurred in all patients despite prophylactic measures (typical symptoms included hypotension, fever, nausea, vomiting, diarrhoea and skin rash). Six out of 16 deteriorated during the course of treatment but this alteration was transient in three. Two patients died from complications of severe multiple sclerosis between 9 and 12 months after enrolling in this trial. Overall, the authors were uncertain that the treatment provided any lasting benefit to this group of patients. At the 1 year follow-up examination, of the 15 patients who completed the treatment protocol, four had worsened by ≥ 1.0 EDSS points (including the two deaths), nine were unchanged (EDSS changed by ≤ 0.5 points) and two improved by ≥ 1.0 EDSS point. No conclusions could be reached in the three patients with relapses of whom one each improved, remained stable and deteriorated. A small number of serial MRI scans failed to show an effect on lesion load. Rapid but transient reductions in circulating lymphocytes and their subpopulations were observed. All patients developed high titres of human anti-mouse antibodies. The systemic manifestations of OKT3 administration are known to be cytokine mediated, to correlate with sequential release of circulating TNF-α and IFN-γ followed by IL-6, and to be suppressed with methylprednisolone (Pececs *et al* 1993). Each of the two patients studied by Weinshenker *et al* (1991c) showed a transient surge in circulating TNF-α and IFN-γ on the first day of treatment. Therapy was complicated by oral candidiasis, and two patients were thought on clinical grounds to have aseptic meningitis. Whilst not promoting the continued use of murine monoclonals in multiple sclerosis, Weinshenker *et al* (1991c) advocated the development of more specific and less toxic reagents, manipulated to restrict their immunogenicity.

Anti-CD4

The first reported study using murine anti-CD4 monoclonal antibody therapy in multiple sclerosis (Racadot *et al* 1993) included 21 patients with disease progression or frequent relapse and showed no acute effects (good or bad). Clinical stabilization was claimed for 12 of 20 patients at 3 months and eight of the 20 at 6 months. No new relapses were documented. The reductions in circulating lymphocytes had returned to normal ranges within 90 days. A transient elevation was observed in circulating TNF-α, soluble TNF receptor and IL-6 but not IFN-γ, IL-1 or soluble CD8 and CD4 antigen. Unlike most other investigators, Racadot *et al* (1993) reported a detectable rise in cerebrospinal fluid TNF-α levels.

Lindsey *et al* (1994a) treated 29 patients in an open uncontrolled study with a chimaeric anti-CD4 antibody in doses ranging from 10 to 200 mg given as a single infusion, or over 3 days. The reduction in total circulating lymphocytes was partial and recovered within 6 months. The same pattern was observed for CD4 cells but without complete return to the normal range. Five patients developed anti-murine antibodies. Small improvements were noted in three of 26 patients undergoing clinical evaluation, but the majority remained unchanged (16 patients) or deteriorated (seven patients). Fourteen of 25 patients in whom serial scans were obtained had enhancing lesions on baseline MRI. One hundred enhancing lesions were seen on 91 scans obtained during follow-up, and 17 of 25 patients showed an increase in T_2-weighted lesions. The patients reported minor systemic symptoms and there was an increase in infections requiring treatment.

Most of these patients were subsequently considered for re-treatment on the basis that their CD4 count returned to >300 cells/mm^3 (Lindsey *et al* 1994b). Several were withdrawn or elected not to continue and one died suddenly after aspiration whilst eating. Twenty-one of the original cohort received up to three further treatments (a total of 36 courses were administered), responding with a drop in CD4 count on each occasion and sometimes showing prolonged lymphopenia. There seemed to be no increase in the development of anti-idiotype antibodies with this second exposure. One patient improved, three worsened, 16 remained unchanged and one was lost to follow-up. MRI activity was seen on ten of 16 scans before treatment and on 12 of 26 scans (from 16 patients) at follow-up (six of 17 in the subgroup with persistently low CD4 counts). Other than minor infections, some requiring treatment, and one episode of herpes zoster, there were few complications of repeated treatment. On the basis of these preliminary results, van Oosten *et al* (1997) randomized 71 patients, most with clinical and radiological evidence for disease activity, to treatment with chimaeric anti-CD4 or placebo under double-blind conditions.

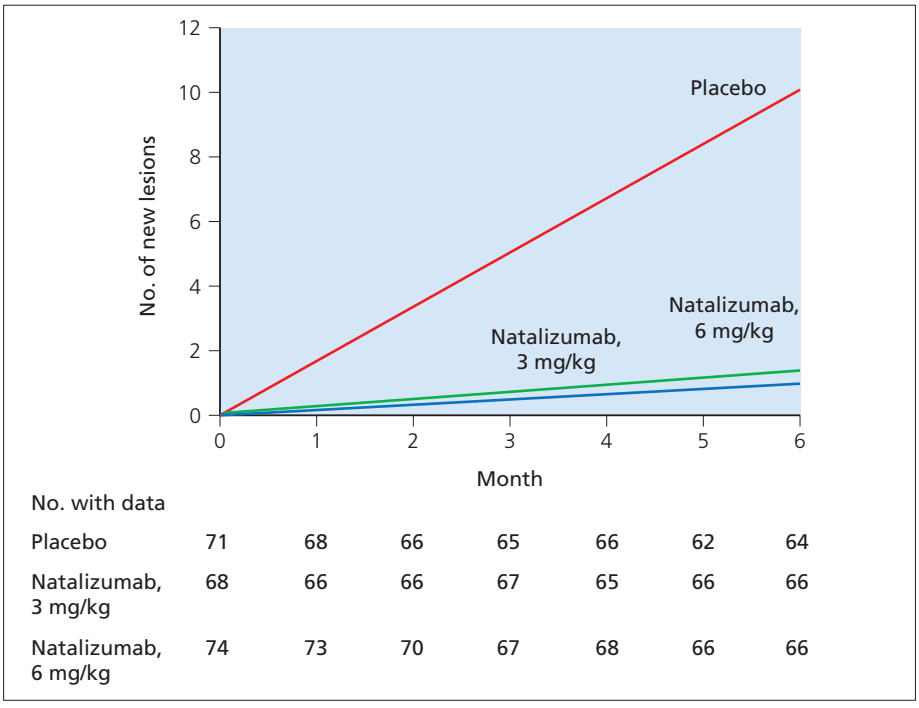
Although circulating CD4 counts were reduced, both groups showed persistent radiological activity (at around 1.5 new lesions per patient per month) although the number of clinical exacerbations was lower, by 41%, in the treated than placebo group. A mild cytokine release syndrome was apparent in these patients leading to withdrawal from the study in a few instances. Serial immunological observations in a subgroup of participants showed, as expected, reduced numbers of $CD4^+$ naive memory cells (which persisted for 12 months after treatment) but there was no effect on serum levels or on mitogen-stimulated release of TNF-α (Llewellyn-Smith *et al* 1997). These blood markers did not correlate with MRI activity.

Natalizumab (anti-VLA4)

Lymphocytes and monocytes express $\alpha_4\beta_1$ integrin on their cell surface. This glycoprotein binds the endothelial VCAM-1 and thereby mediates cell adhesion and transendothelial migration. Natalizumab (initially marketed as Antegren, Elan Pharmaceuticals and Biogen) is a humanized monoclonal antibody that blocks the α_4 integrin adhesion molecule and so reduces cell migration across the blood–brain barrier. Since serial gadolinium-DTPA enhanced MRI scans indicate breakdown of the blood–brain barrier as a consistent feature of new lesions (Kermode *et al* 1990), these properties suggested a potential therapeutic role during the active inflammatory stage of active multiple sclerosis. Data from the experimental autoimmune encephalomyelitis model of multiple sclerosis (Engelhardt *et al* 1998; van der Laan *et al* 2002) indicated that adhesion molecule inhibition might have therapeutic effects in inflammatory brain disease independent of the effect on cell migration. Natalizumab administration reduced new MRI activity in a placebo-controlled pilot study where two intravenous doses were given 1 month apart (Tubridy *et al* 1999; and see Schwid and Noseworthy 1999).

Against this background, D.H. Miller *et al* (2003a) reported a phase two randomized, double-blind, placebo-controlled study comparing two doses of natalizumab (3 and 6 mg/kg) administered intravenously once monthly for 6 months in 213 patients with relapsing–remitting multiple sclerosis. Both doses favourably influenced the primary end point (number of new MR lesions as determined by monthly scanning). Significantly fewer patients reported clinical relapses in the active treatment arms at 6 months (relapse-free: placebo, 62%; both active groups, 81%; $p = 0.02$: Figure 18.44). However, the apparent benefit of these treatments was not prolonged beyond the period of treatment. During the subsequent 6 months of follow-up, during which patients were untreated, those previously randomized both to the placebo and natalizumab groups, had essentially identical numbers of relapses and amounts of MRI activity. Treatment was well tolerated although there were a few allergic responses (including one episode of anaphylaxis causing bronchospasm and urticaria that responded quickly to emergency treatment with antihistamines), and perhaps a minor trend suggesting increased risk of infection (pharyngitis) in treated subjects. In a follow-up report, Dalton *et al* (2004b) demonstrated that gadolinium enhancing MRI lesions developing in the natalizumab-treated patients were less likely to develop into T_1 hypointense lesions (T_1 black holes) at 1 year than those present in the placebo patients. This report suggests that even a relatively limited period of treatment with this agent might have a degree of prolonged benefit on MRI behaviour. The clinical relevance of this finding remains to be determined.

These encouraging early findings led to further evaluation in two large phase III trials. Nine hundred and forty-two patients with relapsing–remitting multiple sclerosis, who had not received any other drug treatment for at least 6 months, were randomized to treatment with either natalizumab (300 mg) or placebo intravenously every 4 weeks for 28 months. A second placebo-controlled trial was designed to determine whether



No. with data							
Placebo	71	68	66	65	66	62	64
Natalizumab, 3 mg/kg	68	66	66	67	65	66	66
Natalizumab, 6 mg/kg	74	73	70	67	68	66	66

Figure 18.44 Treatment of relapsing–remitting multiple sclerosis with intravenous natalizumab (a humanized monoclonal antibody against anti-α_4 integrin) at 3 mg/kg (blue line) and 6 mg/kg (green line). Cumulative mean number of new gadolinium-enhancing lesions on MRI while on treatment. However, in the subsequent 6 months, upon discontinuing treatment, the patients originally treated with the active antibody had equal numbers of relapses and MRI markers of disease activity to those originally randomized to placebo. Adapted from D.H. Miller *et al* (2003a). © 2003, reproduced with permission of the Massachusetts Medical Society.

prolonged administration of natalizumab provides additional benefit to weekly IFN-β1a in 1171 individuals who have already experienced at least one episode whilst on IFN-β1a. Preliminary data on safety, immunogenicity, pharmacokinetics and pharmacodynamics indicated that there were no unfavourable interactions between these therapeutic agents (Vollmer *et al* 2004a). In a similar but smaller trial, investigators randomized 110 patients treated with glatiramer acetate to monthly doses either of natalizumab or placebo for a period of 6 months.

Preliminary results of the first two studies described above, after patients had received treatment for a median duration of 13 months, led the Food and Drug Administration (*http://www.fda.gov/*) to license natalizumab (Tysabri) 300 mg by intravenous infusion every 4 weeks, late in 2004 for the 'reduction of clinical exacerbations in patients with relapsing forms of multiple sclerosis'. The advice on use in pregnancy is ambiguous ('only if clearly needed'); administration to individuals aged under 18 years is contraindicated; advice on the upper age limit is noncommittal. Although experience beyond 13 months was limited at that time, the only adverse effects of note were headache, arthralgia, infections and hypersensitivity reactions but these were infrequent and rarely limiting. In study 1, the annualized relapse rate was 0.25 in individuals receiving natalizumab compared to 0.74 in the placebo group; the percentages of patients remaining relapse free were 76% and 53%, respectively. In study 2, annualized relapse rate was 0.36 in patients receiving natalizumab compared to 0.78 (the same as placebo-treated cases from study 1) in those only being treated with IFN-β1a; the percentages of patients remaining relapse free were 67% and 46%, respectively – even less than the placebo rate for these individuals receiving IFN-β1a. As expected, the clinical results were matched by comparable reductions in disease activity using imaging surrogates. Again, there was no difference in the proportion or number of cases showing activity comparing the placebo group of study 1 and the IFN-β1a-only group of study 2 but this may reflect differences in the study populations. About 6% of patients developed a persistent antibody response to natalizumab that was associated with an apparent loss of clinical effectiveness. Clearly, these data do not provide support that IFN-β1a is effective in reducing clinical or MRI evidence of disease activity in patients who continue to report clinical relapses while receiving this agent.

The patients involved in the 2 year placebo-controlled trials are being followed in an extension study while on natalizumab; in order to obtain long-term data on effectiveness, tolerability and safety in addition to immunogenicity. The intention was to follow what happens to these patients in the 6–12 months after infusions cease, so as to determine whether this more prolonged antibody administration proves more durable against clinical and MRI indicators of disease activity than the results reported to date.

On 28th February 2005 the sponsors of Tysabri (Biogen Idec and Elan Pharmaceuticals) voluntarily removed this agent from clinical and research trial use because progressive multifocal leukoencephalopathy was reported in two patients treated with the combination of Tysabri and IFN-β1a (Avonex) for more than 2 years. A third case was soon reported in a patient treated with Tysabri for Crohn's disease (eight doses over a period of 18 months), again in the context of a randomized trial; the patient died from what initially was thought to have been a fatal glioma and later confirmed to be progressive multifocal leukoencephalopathy. This patient had been refractory to corticosteroids, azathioprine and other immunosuppressants – perhaps contributing to the risk of additional immunosuppression with this experimental agent. Two additional unconfirmed cases have been subsequently reported in the context of clinical trials for multiple sclerosis but, at the time of writing, the details are scarce. Tysabri-treated patients from these trials are now under close scrutiny to detect progressive multifocal leukoencephalopathy as early as possible and investigators are reviewing the available data to understand the mechanism(s) of presumed reactivation of the JC virus in this setting. As highlighted earlier, these events remind us of the potential risks inherent in clinical trials (Drazen 2005). It remains uncertain that this once-approved therapeutic agent will resurface for use in multiple sclerosis and other inflammatory disorders.

Anti-Vβ5.2/5.3⁺ T cells

In a study designed to determine whether administration of the humanized monoclonal antibody ATM-027 (with specificity for Vβ5.2/5.3$^+$ T cells) would reduce MRI measures of disease activity, Killestein *et al* (2002b) stratified relapsing–remitting patients by HLA-DR2 status to receive monthly intravenous infusions either of the antibody (n = 47) or placebo (n = 12). The dose was titrated to deplete the target T cells. Treatment successfully suppressed the Vβ5.2/5.3$^+$ T-cell population and was well tolerated. There was a trend suggesting a reduction in MRI activity (lesion count, volume of enhancing lesions) but this result did not achieve the goal of the study.

Anti-CD52

Campath-1H may emerge as an important treatment for multiple sclerosis. From the clinical science perspective, its credentials are already established. Clinical observations provided the stimulus for basic research that has illuminated key aspects of the pathogenesis (Coles *et al* 1999a; Moreau *et al* 1996; Redford *et al* 1997; K.J. Smith *et al* 2001; Wilkins *et al* 2003). In turn, these are now being recycled into clinical practice and with provisionally encouraging results. Campath-1H is a humanized monoclonal antibody suitable for therapeutic use that targets the CD52 antigen present on all lymphocytes and a proportion of monocytes. As a result of its isotype, Campath-1H is exceptionally good at activating complement and mediating antibody-dependent cell-mediated cytotoxicity (M.Q. Xia *et al* 1993). CD52 does not lose its potential for lysis through modulation by antibody. Lymphopenia is rapid and prolonged following a pulse of treatment since the CD52 antigen is expressed in high density on the target cell membrane (Hale *et al* 1990). The median times to recovery of baseline counts for CD3, CD4, CD8 and total lymphocytes are 51, 61, 30 and 66 months, respectively. Conversely, B-cell numbers return more rapidly and tend to overshoot above baseline but rarely rise above the upper limit of the normal range. Although a single treatment does not elicit an anti-globulin response, this may not be the case if repeated courses of antibody are given. Campath-1H has been studied in three cohorts of patients with multiple sclerosis treated on an open label basis.

The change in MRI evidence for disease activity following treatment with Campath-1H established that a reduction in the

availability of circulating lymphocytes is associated with a more or less complete cessation in new lesion formation and prompted the further evaluation of Campath-1H as a possible disease-modifying treatment (Moreau *et al* 1994). A second cohort of 36 patients with secondary progressive multiple sclerosis (duration of the progressive phase, 3.6 ± 2.6 years; mean EDSS 5.8 ± 0.8; increase in disability in the year before treatment, ≥ 1 EDSS point; annual relapse rate, 0.7 per patient per year) confirmed that radiological evidence for disease activity was suppressed by >90% for at least 18 months (Coles *et al* 1999a; Paollilo *et al* 1999). Relapse rate, expected to decline as part of the natural history of multiple sclerosis in the secondary progressive phase, changed from 0.7 per patient per year before treatment to an annualized rate of 0.02 per patient per year at mean follow-up of 6.7 (SD ± 2.1) years. When 13 patients from this original cohort were re-examined 5.8 years (± 0.5) after their last scan (which was itself 18 months after Campath-1H), there was no evidence for an increase in proton density or T_1 lesion volume in the intervening period.

However, dissociation emerged between this suppression of inflammation and disease progression. Disability increased by +0.2 EDSS points per patient per year. Although this represents a statistically significant reduction in rate of progression compared to the year before treatment ($p < 0.001$), the toll of incremental progression over time has led to substantial accumulation of disability with no overall benefit from treatment (Figure 18.45). Disease progression was associated with brain atrophy. Patients who progressed from baseline at the first follow-up interval (18 months) showed reduced brain volume at the time of treatment with Campath-1H by comparison with patients showing initial stability of clinical progression. Those who progressed early had most inflammatory activity prior to treatment. Furthermore, despite continued suppression of cerebral inflammatory activity, this poor prognosis group with atrophy at the time of treatment and early disease progression demonstrated sustained reduction in brain volume and altered MR spectroscopy (*N*-methyl-aspartate) indicating progressive axonal loss. After 7.5 years, mean percentage change in cerebral volume was –0.48% (± 0.46) per year. The mean absolute change was –1.37 (± 1.28) mL/year ($p = 0.002$). Two patients in this group had measurable cerebral atrophy despite clinical stability. Early loss of brain volume was an indicator of sustained atrophy. The six of 13 patients who had already shown increased cerebral atrophy at 18 months after Campath-1H had a mean further loss of 2.13 mL per year (± 0.65), compared to only 0.7 (± 1.4) mL per year in those whose cerebral volume was stable for the initial 18 months after treatment ($p = 0.042$). The lesson is clear. Once the cascade of events leading to tissue injury is established, effective suppression of inflammation does not limit brain atrophy or protect from clinical progression.

Against this background, a third cohort consisted of 22 patients with active relapsing–remitting multiple sclerosis, a short clinical history and no disease progression (Coles *et al* 2005). As a group, they had experienced a total of 133 relapses over 60 patient-years of combined disease history before treatment, giving an annual relapse rate of 2.2 per patient. This rose to 2.94 per patient in the year before Campath-1H. The cohort included 17 drug naive patients and five who had already failed treatment with IFN-β. After treatment this cohort has had five investigator-confirmed episodes, giving a relapse rate of 0.14, and representing a 94% reduction in relapse rate (Figure 18.46). By comparison with many of the pretreatment episodes, all but one was clinically mild with full spontaneous recovery and leaving no stepwise increase in EDSS.

It is instructive to compare the accumulation of disability in the relapsing and progressive groups (Figure 18.47). In the year before treatment, the relapsing patients showed a mean annual increase of +2.2 EDSS points. Mean annualized changes over the periods 0–6, 6–12 and 12–24 months were –2.4, –0.6 and –0.4, respectively. This compares with –3.8, –0.6 and –0.2 in the relapsing–remitting cohort (excluding the more advanced group of patients who had failed previous treatment with IFN-β). Nine of 15 patients observed at 1 year had an improved EDSS. All but one of the others was stable, and the mean effect was an improvement by 1.2 points compared to baseline. This improvement was sustained in the nine patients observed at 24 months, whose mean EDSS was –1.3 points from baseline. One patient had a sustained deterioration from EDSS 6.0 to 6.5 within the first 3 months after Campath-1H, but no subsequent change in disability. This stabilization of disability stands in marked contrast to the group with secondary progressive multiple sclerosis.

Patients treated for multiple sclerosis with Campath-1H experience an acute cytokine release syndrome with severe but temporary rehearsal of previous clinical features - specific manifestations varying with previous clinical features (see Chapters 10 and 13; Figure 18.48; Moreau *et al* 1996). Pretreatment with corticosteroids abolishes or minimizes these neurological exacerbations. Infections that may represent adverse effects of Campath-1H are mild and relatively infrequent given the profound and prolonged depletion of lymphocytes. These include spirochaetal gingivitis (at 10 days), measles (at 11 days), herpes zoster (three instances; at 6 and 9 months, respectively), varicella zoster (at 2 years), recurrent aphthous mouth ulcers (from 6–9 months), pyogenic granuloma (at 22 months), and listeria meningitis after eating soft cheese at 2 weeks. One patient with secondary progressive multiple sclerosis (EDSS 8.5) died of sepsis 7 years after Campath-1H treatment.

The principal adverse effect of Campath-1H therapy in patients with multiple sclerosis is Graves' disease (Coles *et al* 1999b). One patient had experienced Graves' disease prior to Campath-1H treatment and, to date, 15 new cases have been observed after treatment in the remaining 57 patients (27%), with one additional case of autoimmune hypothyroidism. One patient in the relapsing–remitting group developed acute renal failure as a result of Goodpasture's syndrome, with no lung involvement. This occurred 10 months after treatment with Campath-1H and was associated with the development of high titre anti-glomerular basement membrane antibodies, which were not detectable in serum taken before Campath-1H treatment, nor 1 month before her illness. Systematic screening of sera from all other patients for autoantibodies against glomerular basement membrane, reticulin, gastric parietal cell, endomysial, anti-acetylcholine receptor and anti-voltage gated calcium channel have shown no abnormalities. One patient has developed positive anti-double-stranded DNA antibodies without any clinical evidence of systemic lupus erythematosus, impaired renal function, or arthritis. Another patient with a positive family history of coeliac disease had elevated positive IgA and IgG anti-gliadin antibodies, without IgA tissue transglutaminase antibodies, in a single serum sample at 1 month after Campath-1H.

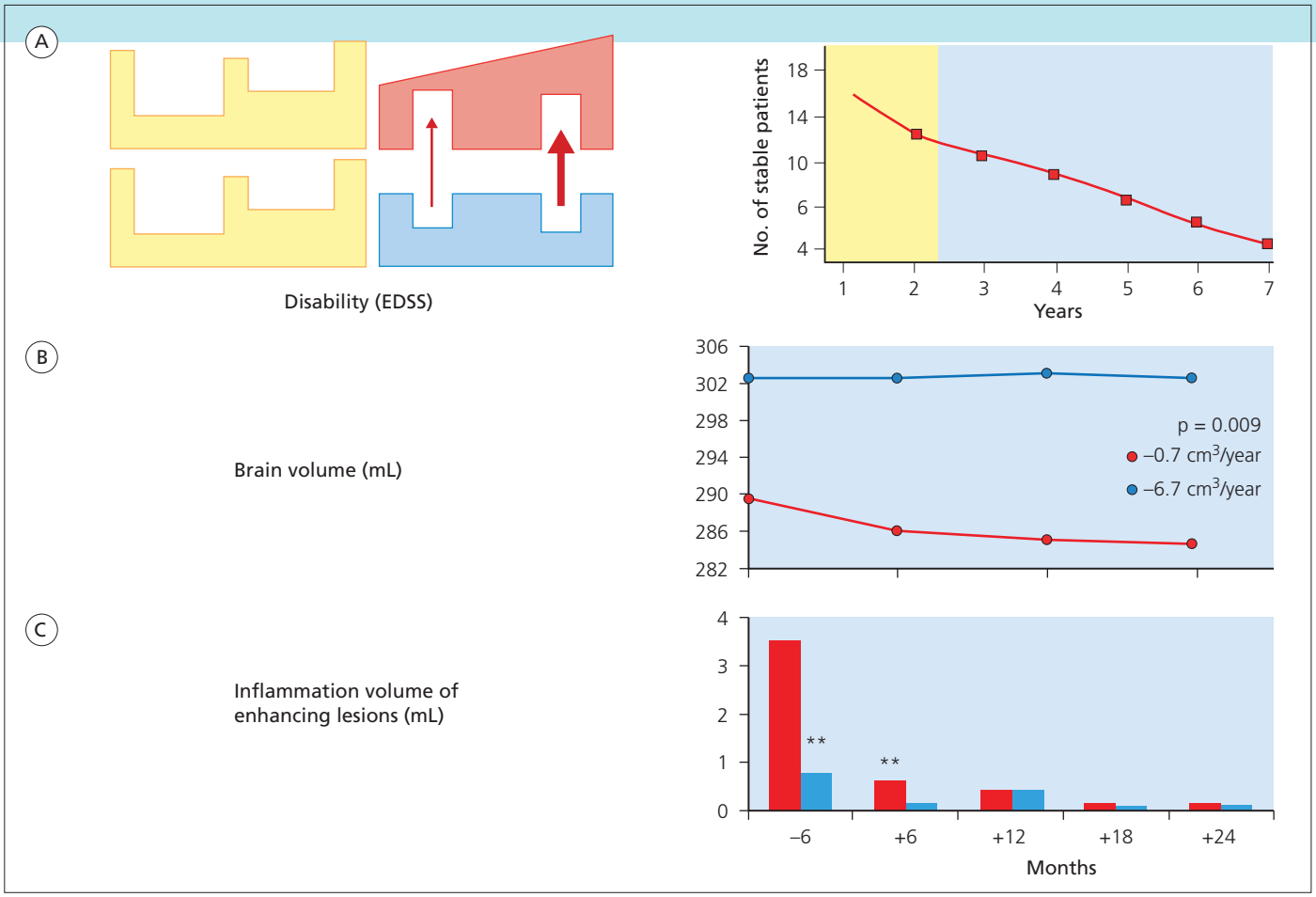


Figure 18.45 Correlation between brain atrophy and progression of disability in patients with secondary progressive multiple sclerosis showing substantial reduction in new lesions after treatment with Campath-1H. Adapted from Coles *et al* (1999a). © 1999, reproduced with permission of John Wiley & Sons.

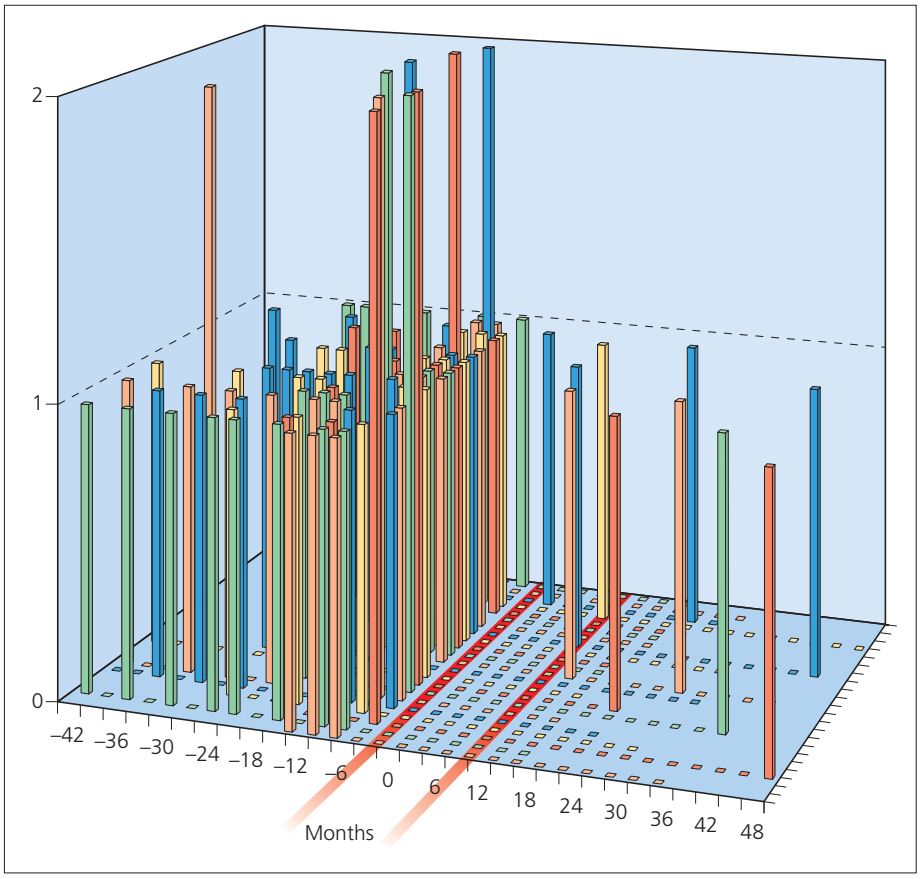


Figure 18.46 Reduction in new episodes following treatment with Campath-1H in patients with active relapsing–remitting multiple sclerosis. Adapted from Coles *et al* (2005).

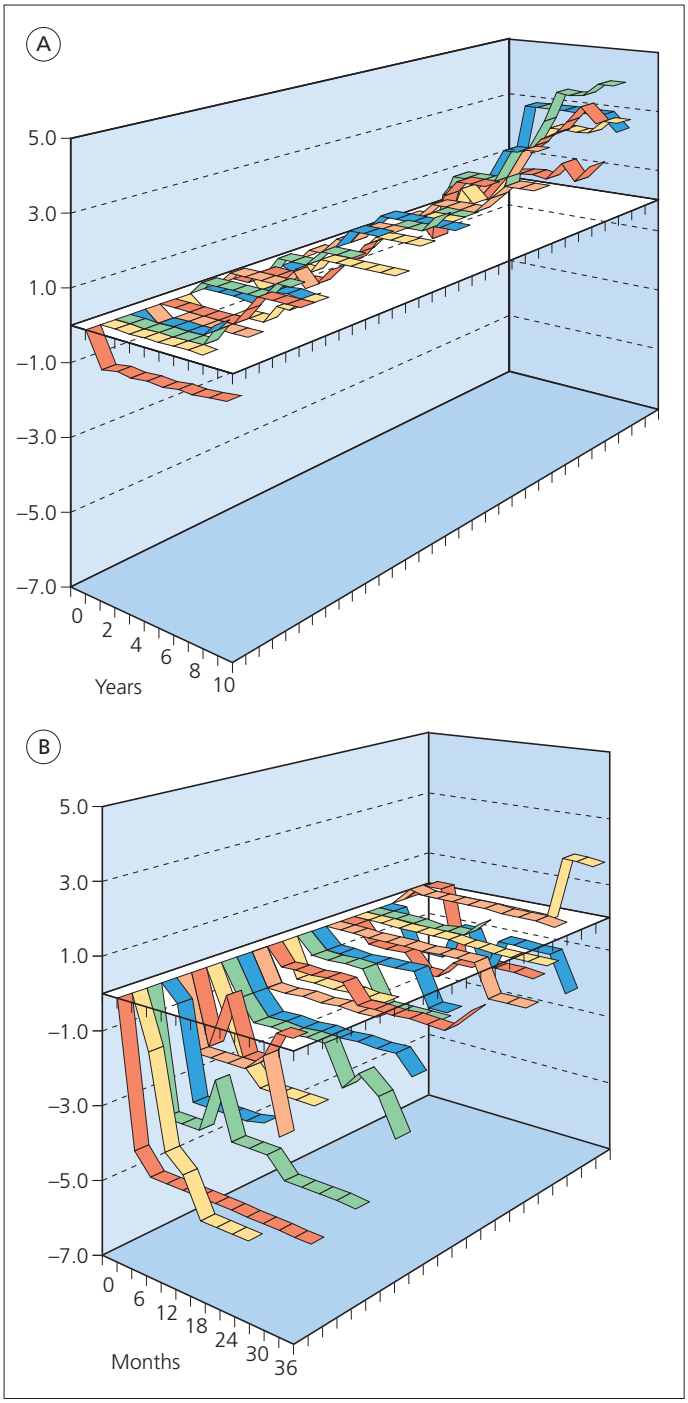


Figure 18.47 Comparison of serial change in disability (EDSS) in 36 patients with secondary progressive multiple sclerosis and 22 with early active relapsing–remitting disease. Adapted from Coles *et al* (2005).

These were undetectable in both the subsequent serum samples and those taken before treatment. Recruitment closed in April 2004 for a phase II multicentre randomized study comparing two doses of Campath-1H (60 mg and 120 mg over 5 days at baseline, repeated at 1 and 2 years) with IFN-β1a (Rebif; 22 μg three times weekly increasing at 1 month to 44 μg three times weekly by subcutaneous injection) in patients with early clinically active relapsing–remitting multiple sclerosis. The primary outcome is time to sustained disability as determined at 3 years. A press release issued by the sponsors in September 2005 reporting the first interim analysis indicates at least a 75% treatment effect on relapse rate, and >60% on sustained accumulation of disability, each at 1 year, compared with Rebif. These preliminary results appear to confirm the high efficacy of Campath-1H but, as before, the major adverse effect relates to autoimmunity with three cases of idiopathic thrombocytopaenic purpura, one of which proved fatal

Anti-CD25 (daclizumab)

There are few studies that systematically address the management of patients failing to respond adequately to approved therapies. In an uncontrolled series, Rose *et al* (2004) treated 19 patients, 17 of whom were not responding to other therapies, for between 5 and 25 months with daclizumab and claimed that all showed reduced MRI activity, compared with pre-treatment images, and 'sustained clinical improvement (10) or 'stability' (9). In a recent report, Bielekova *et al* (2004) administered a humanized monoclonal antibody (daclizumab) directed against the IL-2 receptor on activated T cells (IL-2Rα-chain; CD 25) to 11 patients with multiple sclerosis who appeared not to be responding to IFN-β1b treatment. All patients continued to receive IFN-β1b therapy during this study. 'Failure to respond' was defined as either one or more relapses or continued progression of ≥ 1.0 EDSS worsening over a period of 18 months on IFN-β1b treatment. Patients were selected for participation if they demonstrated ≥ 0.67 new MRI lesions per month during a 4-month period on IFN-β1b treatment. Treatment was given as 1.0 mg/kg per intravenous dose at baseline and week two, and then five additional infusions given at 4-weekly intervals. This agent was well tolerated although there were more infections and liver enzyme elevation over the period during which the antibody was given. There was a 78% reduction in new contrast enhancing lesions compared with baseline that began approximately 6–8 weeks after the first antibody infusion. One patient seemed to respond only to a higher dose (2 mg/kg per dose administered every 2 weeks). Secondary measures of benefit included a reduced relapse rate, better motor performance on the nine-hole peg test, improved scores on the Scripps Neurological Rating Scale, and reduced volume of contrast enhancing lesions. Further studies are planned.

T-cell vaccination

One therapeutic approach has been to eliminate antigen-specific autoreactive T cells by vaccination with X-irradiated cells primed against myelin basic protein. It was J. Zhang *et al* (1993) who first showed that inoculation of myelin basic protein reactive T cells induces responses that deplete circulating antigen-specific T cells, confirming that clonotypic interactions regulating autoreactive lymphocytes can be induced in humans by T-cell vaccination. Subsequently, in a small pilot study involving eight patients, five showed a reduction in relapses from a total of 16 to three in the 2 years before and after treatment, whereas controls showed no apparent reduction (12 and 10 before and after treatment). These clinical changes were accompanied by a difference in MRI lesion load of +8% and +39.5%, respectively. Clinical and MR indices of disease activity worsened in three patients in whom

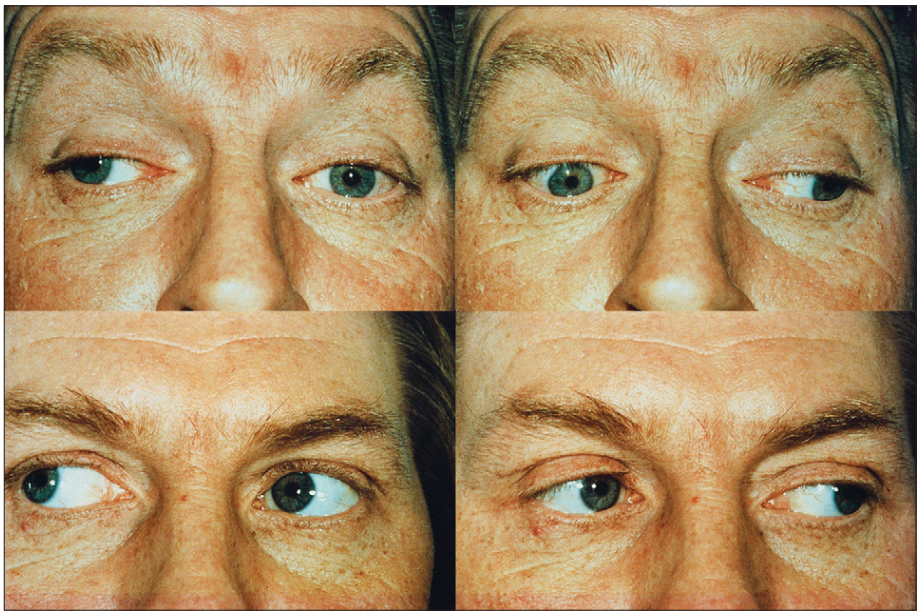


Figure 18.48 Recurrence of internuclear ophthalmoplegia with complete recovery developing in a patient during (top) and after (bottom) the first infusion of CAMPATH-1H. From Moreau *et al* (1996) with permission.

autoreactive T cells (showing different antigenic specificity) reappeared after vaccination (Medaer *et al* 1995).

Building on their earlier experience with experimental autoimmune encephalomyelitis (see Chapter 11) and clinical laboratory studies, Vandenbark *et al* (1996a) immunized 23 HLA-DRB1*1501-positive patients with T-cell receptor Vβ5.2 (residues 38–58 in two variations, with and without a tyrosine to threonine substitution at position 49), or placebo (n = 6) peptides on 14 occasions over 1 year. T-cell responses were more predictable and rapid with the substituted than natural peptide but were difficult to sustain in both groups. Several who were vaccinated continued to show T-cell reactivity on completion. However, there was a reduction in myelin basic protein reactivity which also correlated with altered disease progression. An unusually high number of patients with primary progressive multiple sclerosis was included (eight of 23 patients) and neither these nor the secondary progressive cases showed a clear clinical benefit (or deterioration) from the vaccination protocol (those who responded immunologically remained unchanged by comparison with all other participants, both placebo-treated and nonresponders; p = 0.02). Peptide-specific T-cell clones tended to show Th2 cytokine profiles (predominant production of IL-10) in contrast to the Th1 features of their myelin basic protein-specific T-cell clones.

Bone marrow and stem cell transplantation

Bone marrow transplantation following immune ablation has received much attention in recent years. More research is needed before it is clear whether this is a useful approach to treatment, and sufficiently safe to justify whatever clinical dividend emerges in due course. Currently patients either with advanced secondary progressive multiple sclerosis or refractory, aggressive relapsing–remitting disease are being assessed. If efficacy is established, the next step may be to assess whether patients who are at an earlier stage of the disease, but can genuinely be predicted to have a poor prognosis, should be selected for further trials. In the context of multiple sclerosis, the term stem cell transplantation is currently used primarily to refer either to bone marrow or peripheral blood autologous stem cell transplantation applied in the setting of immune system ablation. Experimental work with neural stem cells is moving quickly in model systems but is not yet applied to patients. The rationale for stem cell transplantation in all immune-mediated disorders is the premise that after near complete ablation of the host immune system (full ablation is not currently possible), the reconstituted immune system will be reprogrammed, resulting either in prolonged remission or amelioration of immune-mediated attack on the host. However, it remains to be established whether therapy depends more on the immunosuppressive induction with autologous stem cell rescue than these strategies for immune tolerance to autoantigens. Whatever the precise mechanisms, preliminary evidence in experimental animal model systems and multiple sclerosis is considered promising (Burt *et al* 1995; 1997).

Allogenic stem cell transplantation requires an HLA identical donor and, as such, has rarely been feasible for patients with multiple sclerosis. With advances in umbilical cord blood screening methods for bone marrow donors and cord blood banks, it will soon theoretically be possible to identify HLA compatible donors for haematopoietic stem cell transplantation (Laughlin *et al* 2001). Bone marrow harvesting requires a general anaesthetic, yields few T cells and is associated with a longer reconstitution time. Currently, most programmes therefore harvest autologuous stem cells from peripheral blood (as opposed to bone marrow) since this requires only a brief exposure to the risks of bone marrow suppression (Comi *et al* 2000; Tyndall and Koike 2002). Currently, peripheral blood stem cell harvesting is achieved using high-dose cyclophosphamide (2–4 g/m^2) either alone or with granulocyte colony-stimulating factor (G-CSF). G-CSF has been used without cyclophosphamide but may increase the likelihood of triggering an exacerbation of multiple sclerosis. This occurred in four of ten

patients receiving G-CSF for peripheral blood stem cell harvesting (Openshaw *et al* 2000a). Three patients responded to methylprednisolone but one relapse proved fatal. These investigators reportedly now administer methylprednisolone together with recombinant G-CSF and do not use G-CSF after the patient is transplanted. There are several options for cytotoxic drug conditioning, including BEAM (*B*CNU, *E*toposide, cytosine *A*rabinoside, and *M*elphalan) alone or with anti-thymocyte globulin. Others use cyclophosphamide together with total body irradiation and a combination of busulfan and cyclophosphamide. The field has moved away from T-cell purging as there is no clear advantage and the risks of infection in the setting of T-cell depletion are high.

During the mobilization phase, patients may experience fever, seizures and infection. Allergic reactions to cyclophosphamide, G-CSF or the stem cells may occur during the intervention. Following transplantation, patients can experience allergic responses to anti-thymocyte globulin. Mucosal infections, prolonged fever, bleeding, neutropenia, thrombocytopenia, neurotoxicity and autoimmune thyroiditis (as with Campath-1H) are all encountered. Late complications, especially in T-cell-depleted grafts, include serious infections (such as aspergillosis), veno-occlusive liver disease, thrombotic thrombocytopenic purpura, hypogonadism, cataract formation, and the development of malignancy related to the prolonged period of immunosuppression (Fassas *et al* 2000). Although autologous peripheral blood stem cell transplantation has a lower risk than allogenic transplantation, mortality rates are still reported to be in the 5% range or slightly higher. This relatively high risk of a fatal complication for an experimental therapy given in the context of a chronic, rarely life-threatening disorder places the burden on proof of superiority for those conducting this work.

The numbers of cases treated worldwide is ever increasing. In 2000, it was estimated that 74 patients with multiple sclerosis had been transplanted. This had risen to 109 by the third quarter of 2002, and approximately 200 people with multiple

Table 18.9 Published results with haematopoietic stem cell transplantation in multiple sclerosis

Investigator	Conditioning and immune ablation	Comments
Mancardi *et al* 2001 (ten patients; five Italian sites)	30–40 days following BEAM	Median follow-up only 18 months. Most stable. No Gd+ or new T_2 lesions. Atrophy (1 year) and oligoclonal bands continued at 2 years
Kozák *et al* 2002 (15 patients)	BEAM-ATG. 9/15 also received *ex vivo* T-cell depletion of graft	One death from progressive multiple sclerosis. Median follow-up 20 months with 11/15 stable or improved
Saiz *et al* 2004 (15 patients)	BCNU, high-dose cyclophosphamide, ATG and T-cell-depleted grafts	3 year median follow-up: 46% free of disease activity. No deaths. 4/14 continued to relapse (3 of these at multiple times). MRI no new lesions but atrophy continued
Openshaw *et al* 2000b (five patients)	Busulfan, cyclophosphamide and T-cell-depleted blood autografts	One died early post-transplant; histology showed macrophages but few T cells surrounding demyelinated plaques
Nash *et al* 2003 (26 patients; four United States sites)	Prednisone 1 mg/kg/day by mouth, TBI 2Gy × 4 doses, cyclophosphamide 60 mg/kg × 2 doses, horse ATG 15 mg/kg/daily × 6 doses, GCSF 5 μg/kg/daily by intravenous injection	27% progressed by ≥ 1.0 EDSS at 3 years. Four new Gd+ lesions. Nine of 12 still had oligoclonal bands. One died with EBV-PTLD. Two relapses during mobilization, one proving fatal; 91% survival at 3 years
Burt *et al* 2003 (21 patients; three United States sites)	Cyclophosphamide 60 mg/kg iv, TBI with lung shield, 150 cGy bid on days –3, –2, –1	No transplantation-related deaths. Two died from progressive multiple sclerosis after 13–18 months. Eight of 12 at EDSS >6 worsened. All nine of nine at EDSS < 6 remained stable
Kimiskidis *et al* 2002 (35 patients)	Cyclophosphamide, G-CSF, BEAM, busulfan	G-CSF may have caused radiological deterioration. Subclinical MRI activity persisted in five patients. MRI atrophy progressed at 12 and 24 months. Two cases developed post-transplantation autoimmunity: thyroiditis (1) and refractory factor VIII-inhibitor (one with massive haemorrhage and death). Progression-free survival, 67% at 5 years
Fassas *et al* 2002 (85 patients; nine European sites and one United States site)	BEAM for 54/85 93% peripheral blood stem cell transplants (BMT 7%) 60% had *ex vivo* graft T-cell depletion	Median 16 months follow-up. 27% worsened in early post-transplant period. Seven of 85 (8.2%) died; two from progressive multiple sclerosis with high pretransplantation EDSS scores; five from toxic causes – four infections and one from heart failure. 3 year death rate was 10%; 20% progressed and 21% improved by ≥1.0 EDSS. MRI active after TPT in 8%. 74% progression-free survival at 36 months

BEAM = BCNU, etoposide, cytosine arabinoside, melphalan, rabbit ATG (anti-thymocyte globulin); TBI = total body irradiation; G-CSF = recombinant human granulocyte colony-stimulating factor; PTLD = post-transplantation lymphoproliferative disorder; EBMT Study = European Group for Blood and Marrow Transplantation Study.

sclerosis had been transplanted by mid-2003. A position paper summarizing the opinion of selected European multiple sclerosis specialists has been published making recommendations for each step in this complex therapeutic programme (Comi *et al* 2000). The published results to date are summarized in Table 18.9. As noted, the numbers are small, the follow-up is modest and the evidence for clinical benefit is minimal to date. Several studies have shown MRI evidence for stability or apparent improvement, although serial MRI studies have shown that cerebral atrophy continues to progress after transplantation. Again, it is unclear to what extent the reduction in new MRI lesions relates to the transplant procedure rather than the profound degree of immunosuppression associated with induction.

In the trial reported by Nash *et al* (2003), death from post-transplantation lymphoproliferative disorder was attributed to a change from horse to rabbit anti-thymocyte globulin in the high-dose immunosuppressive therapy protocol. A second death was attributed to a relapse of multiple sclerosis during mobilization (another episode in a second patient during mobilization reversed within 6 months). Thirteen of the first 18 patients developed a fever and rash, sometimes associated with neurological worsening ('engraftment syndrome'). Burt *et al* (2003) reported two late multiple sclerosis-related deaths, and EDSS progression in eight of 12 patients with baseline EDSS scores of 6.0 or higher. They concluded that intense immunosuppression with total body irradiation and haematopoietic stem cell transplantation should not be offered to patients with advanced progressive multiple sclerosis. Conversely, in a retrospective review of bone marrow transplantation, Fassas and Kimiskidis (2003) conclude that the early results are encouraging despite the morbidity and mortality experienced in their protocol. In a recent update of the series from Barcelona, Saiz *et al* (2004) reported on their experience of autologous stem cell transplantation after a course of high-dose chemotherapy. As outlined in the accompanying editorial (Freedman and Atkins 2004), at 3 years median follow-up, four of 14 patients continued to experience relapses (several each in three individuals) suggesting incomplete or ineffective suppression of disease activity although 46% were disease free. This protocol seemingly prevented the development of new contrast enhancing lesions and was followed by reductions in T_2 lesion load. In parallel, however, there was progressive brain atrophy. It remains to be determined whether the reduction in brain volume reflects true progressive atrophy or is fully explained by a reduction in active inflammation. The current status of autologous haematopoietic stem cell transplantation in multiple sclerosis is reviewed elsewhere (Blanco et *al* 2005; Burt *et al* 2005). Muraro *et al* (2005) recently reported that there is an important change in the immune profile of T cells 2 years after stem cell transplantation in patients with multiple sclerosis. Post-transplantation there are fewer memory T cells and a greater diversity of expressed T cell receptors, suggesting that delayed benefit may extend beyond that explained by lymphocyte depletion. The trials in progress will bring more insights but each is relatively small and insufficiently powered to prove definitive.

AGENTS INHIBITING MACROPHAGES AND THEIR MEDIATORS

Drugs that inhibit the function of macrophages (and microglia), or the release of their mediators, have been evaluated in multiple sclerosis although it is unclear whether these studies are primarily motivated by attempts to modify the course of the illness or merely to suppress symptoms.

Monoclonal antibodies targeted against TNF-α have been used in rheumatoid arthritis and appear to stabilize joint symptoms for several months. We have used very short pulses of humanized soluble TNF receptor for the specific purpose of suppressing the cytokine release syndrome associated with the use of Campath-1H without apparent benefit or adverse effect (Coles *et al* 1999a). In a randomized, double-blind, placebo-controlled study of a recombinant soluble TNF-α receptor p55 immunoglobulin fusion protein (lenercept), Arnason *et al* (1999) demonstrated that this agent is associated with an increase in disease activity (earlier, more frequent and possibly more severe clinical relapses) than placebo (Table 18.10). The drug was poorly tolerated (headaches, nausea, abdominal pain; Schwid and Noseworthy 1999). A previous small study had also demonstrated an increase in MRI markers of disease activity in

Table 18.10 Number, duration and annual rate of exacerbations during the Lenercept multiple sclerosis trial

No. of patients	Placebo 43	Lenercept (mg) 44 (10 mg)	40 (50 mg)	40 (100 mg)	p value
Patients with ≥1 exacerbation through week 24	15	21	28	27	0.003[a]
Patients with ≥1 exacerbation through week 48	22	26	32	32	0.007[b]
Exacerbations with onset ≤ week 24	22	28	37	33	
Duration (days) of these exacerbations	28.3	38.6	41.6	42.0	0.62[c]
Range (median)	28 (1–91)	31 (6–189)	31 (6–201)	25 (4–261)	
Annualized exacerbation rate	0.98	1.0	1.64	1.47	

a Chi-square tests: global.
b Kruskal–Wallis test.
c Kaplan–Meier (KM) (means and medians are estimated from the KM curves).

response to anti-TNF-α monoclonal antibody (van Oosten *et al* 1996b). In addition, 17 patients are reported to have developed signs and symptoms suggesting central nervous system demyelination after treatment with the anti-TNF-α agent etanercept, and two patients have had similar reactions to infliximab administration (Mohan *et al* 2001). As such, despite the theoretical arguments in favour of its use, anti-TNF-α strategies do not appear to have a therapeutic future in multiple sclerosis.

A few preliminary results are available on the use of macrophage inhibitors in multiple sclerosis but the choice (or availability) of agents is such that their therapeutic role remains largely unexplored. Deoxyspergualin suppresses the maturation of lymphocytes and also inhibits production of oxygen radicals by macrophages. It received attention amongst multiple sclerosis sufferers through publicity surrounding an individual case and on the basis of effects in experimental autoimmune encephalomyelitis (Schorlemmer and Seiler 1991). Deoxyspergualin was subsequently evaluated in a placebo-controlled study in which 2 or 6 mg/kg deoxyspergualin was given intravenously for 1 month as 5 day pulses (Kappos *et al* 1994). Preliminary results showed no effect on the pretreatment level of disease activity assessed by MRI but the clinical evaluation remains unpublished. Different doses of pentoxifylline were given to 14 patients by L.W. Myers *et al* (1998) to identify that which best suppressed TNF-α production in both a bioassay and enzyme-linked immunosorbent assay. These were sensitive assays since TNF-α was detected in the majority of cerebrospinal fluid samples before treatment. There was no immunological effect of treatment at any dose and almost all the patients deteriorated, objectively and subjectively. MRI abnormalities continued to accumulate. van Oosten *et al* (1996b) also were unable to demonstrate any effect of pentoxifylline (800–1200 mg daily for 4 weeks) on a range of Th1 and Th2 cytokine productions in 20 patients with multiple sclerosis. By contrast, Rieckmann *et al* (1996) showed *in vitro* and *in vivo* suppression by pentoxyfilline (1600 mg/day by oral administration) on TNF-α and IL-12 production, with corresponding stimulation of IL-10 and IL-4 in patients with relapsing–remitting multiple sclerosis.

Nineteen patients (nine with primary progressive and ten with secondary progressive disease) were treated by S.G. Lynch *et al* (1996) using the iron chelator desferroxamine by subcutaneous infusion for 14 days to enhance iron chelation and prevent hydroxyl radical formation. The study was open and uncontrolled and rather little can be learned from the claim that nine, six and three and three, five and six patients improved, were unchanged or worsened by >1 EDSS point at 6 and 12 months, respectively. The same reservations apply to an earlier study of 12 patients with more marked disabilities (EDSS 5.5–8) of whom seven, four and three improved, stabilized or worsened in the 3 months after treatment with desferroxamine (Norstrand and Craelius 1989).

RECENT MISCELLANEOUS TREATMENTS

The National Multiple Sclerosis Society (of the United States) keeps a checklist on trials in progress. The most recent version lists more than 150 current clinical trials (*http://www.nationalmssociety.org/Clinical%20Trials.asp*). Several are likely to be completed in the near future and new options for treatment or fresh insights into preferred strategies for the timing and choice of interventions may be provided. A few new faces are already on the street.

Statins

As outlined in recent editorials (D. Baker *et al* 2003; Neuhaus *et al* 2004), statin drugs are attracting interest in both the scientific and lay literature as potential treatments for multiple sclerosis, and for several reasons. Statins have a wide variety of immunoregulatory effects, are relatively inexpensive, generally well tolerated and available as oral agents. Lovastatin was shown to be partially effective in acute experimental autoimmune encephalomyelitis (Stanislaus *et al* 2001). Neuhaus *et al* (2002) demonstrated that simvastatin, mevastatin and lovastatin each had significant immunosuppressive activities in humans, including treatment-induced reduction in the proliferation of stimulated peripheral blood mononuclear cells, reduced adhesion molecule expression (CD54; ICAM-1), altered Th1/Th2 cytokine profile (paradoxically favouring a so-called 'proinflammatory profile'), reduced matrix metalloproteinase-9 levels and expression of B-cell and T-cell cytokine receptors. In further animal studies, Youssef *et al* (2002) showed that oral atorvastatin promoted a Th2 anti-inflammatory cytokine profile, reduced the expression of MHC class II and costimulatory molecules, and prevented the development of chronic experimental autoimmune encephalomyelitis. There are probably multiple mechanisms whereby statin drugs affect the immune response but inhibition of mevalonate with subsequent reduction in isoprenoids (and, hence, reduced post-translational isoprenylation of proteins) may be important (D. Baker *et al* 2003). In an open label trial of 30 patients with multiple sclerosis, Vollmer *et al* (2004b) reported an effect on contrast enhanced MRI indicators of disease activity (reduction in 44% by number and 40% by volume of contrast enhancing lesions) at months 4, 5 and 6 following the administration of simvastatin (80 mg orally per day) compared with pretreatment data. This small study did not demonstrate a reduction in relapse rate but patients were only followed for 6 months. Being unblinded, the study did not adequately address the possibility of regression to the mean. Exploratory immunological studies did not demonstrate an impressive *in vitro* effect. Much more work is clearly needed to raise the status of statins as a disease-modifying treament in multiple sclerosis.

Estriol

Pregnancy provides an important, though transient, benefit for patients with relapsing–remitting multiple sclerosis (see Chapter 4). This example from nature has long provoked interest in estrogen therapy as a potential treatment option. Sicotte *et al* (2002) completed a small open label trial of daily high-dose oral estriol administration (8 mg/day – an amount designed to simulate pregnancy levels) in 12 women (six each with relapsing–remitting and secondary progressive multiple sclerosis). The relapsing–remitting cohort, but not those with secondary progressive multiple sclerosis, experienced a reduction in MRI evidence for disease activity (number and volume of gadolinium-DTPA enhancing lesions). This result was unexpected since the natural history of gadolinium enhancing lesions appears similar in both clinical subgroups and the response to

other therapies such as IFN-β has been similar. Treated relapsing–remitting patients also demonstrated reduced immune function compared with pretreatment values (such as reduced delayed-type hypersensitivity to tetanus and serum levels of IFN-γ). MRI and immune functions returned to pretreatment levels when estriol was discontinued. The authors do not discuss safety issues other than to say that 'pregnancy levels' of estriol were associated with uterine bleeding requiring endometrial biopsy. They recommend that future trials consider combining estriol with progesterone to prevent uterine endometrial hyperplasia. Other safety issues known to be associated with high-dose estrogen therapy would need to be considered carefully in future trials (including effects on thromboembolic disease, migraine, breast cancer, endometrial hyperplasia and cancer, menstrual irregularity, gallbladder disease, cholestatic jaundice, pancreatitis and hypertension).

Minocycline

Based on its anti-inflammatory properties, acting through the inhibition of matrix metalloproteinases, and evidence for efficacy in experimental autoimmune encephalomyelitis (Popovic *et al* 2002), minocycline seems set for thorough evaluation as a treatment for multiple sclerosis. Metz *et al* (2004) treated 10 patients with relapsing–remitting disease, observed to have a mean number of episodes during the previous 2 years of 2.6 (range 2–4 over the 2 years) with minocycline (100 mg twice daily for 6 months); interim analysis of this uncontrolled series showed no change in the frequency of episodes but mean total enhancing lesion number changed from 1.4 per scan before treatment to 0.2 lesions per scan whilst receiving minocycline, representing > 84% reduction; however, these data (before and after treatment) depended exclusively on the experience of only five patients.

POSTSCRIPT

We have reviewed much that has gone into recent efforts to develop more effective therapies for people with multiple sclerosis. Clearly progress has been made but more is needed. We are cautiously optimistic that the decade ahead will bring even more hopeful news for our patients and trust that progress will accelerate. We say this, fully aware of the vast investment in biomedical research worldwide and the tremendous collaborative spirit that is evident in the work already accomplished and currently under way. We are encouraged by the creativity of the scientific community and anticipate that continued productive collaboration across the research and biotechnology communities will pay further dividends. The currently available, licensed medications demonstrate favourable effects on relapse rates and on MRI indicators of (presumably inflammatory) disease activity. We do not yet know for certain that treatment delays clinical disability progression or the progression of brain and cord atrophy. We strongly suspect that the progression of clinical disability often developing as the years pass is largely attributable to gradual loss of axonal number and function. This assumption brings great hope that meaningful benefits will follow closely on our increased understanding of the factors that determine axonal loss. Until such time as the 'breakthrough' arrives, we must remain objective and humble about what is known and what is not. We must continue to ask the right scientific questions and demand useful answers even if these are hard to acquire. Patients have a right to be informed about the knowledge base and zones of ignorance in multiple sclerosis. They should understand fully the limits of our ability to control the course of their illness and be encouraged to participate actively in debating the merits and demerits of existing and new treatments.

References

Abb L, Schaltenbrand G 1956 Statistische Untersuchung zum Problem der multiplen Sklerose II. *Dtsch Z Nervenheilk* **174**: 199–218

Abbas AK, Murphy KM, Sher A 1996 Functional diversity of helper T lymphocytes. *Nature* **383**: 787–793

Abbott NJ 2002 Astrocyte–endothelial interactions and blood-brain barrier permeability. *J Anat* **200**: 629–638

Abbott RJ, Howe JG, Currie S, Holland J 1982 Multiple sclerosis plaque mimicking tumour on computed tomography. *Br Med J* **285**: 1616–1617

Abbruzzese G, Gandolfo C, Loeb C 1983 Bolus methylprednisolone vs ACTH in the treatment of multiple sclerosis. *Ital J Neurol Sci* **2**: 169–172

Abdul-Majid K-B, Stefferl A, Bourquin C *et al* 2002 Fc receptors are critical for autoimmune inflammatory damage to the central nervous system in experimental autoimmune encephalomyelitis. *Scand J Immunol* **55**: 70–81

Abecasis GR, Cherny SS, Cookson WO, Cardon LR 2002 Merlin – rapid analysis of dense genetic maps using sparse gene flow trees. *Nature Genet* **30**: 97–101

Abele M, Schols L, Schwartz S, Klockgether T 2003 Prevalence of antigliadin antibodies in ataxia patients. *Neurology* **60**: 1566–1568

Abernethy J 1809 *Surgical Observations on the Constitutional Origin and Treatment of Local Disease; and on Aneurisms*. London: Longman, Hurst, Rees & Orme, pp. 91–94

Ablashi DV, Lapps W, Kaplan M *et al* 1998 Human herpesvirus-6 (HHV-6) infection in multiple sclerosis: a preliminary report. *Mult Scler* **4**: 490–496

Aboul-Enein F, Lassmann H 2005 Mitochondrial damage and histotoxic hypoxia: a pathway of tissue injury in inflammatory brain disease? *Acta Neuropathol* **109**: 49–55

Aboul-Enein F, Rauschka H, Kornel B *et al* 2003 Preferential loss of myelin associated glycoprotein reflects hypoxia-like white matter damage in stroke and inflammatory brain diseases. *J Neuropath Exp Neurol* **62**: 25–33

Abraham S, Scheinberg LC, Smith CR, La Rocca NG 1997 Neurologic impairment and disability status in outpatients with multiple sclerosis reporting dysphagia symptomatology. *J Neurolog Rehab* **11**: 7–13

Abramsky O 1994 Pregnancy and multiple sclerosis. *Ann Neurol* **36 (Suppl)**: 39–41

Abramsky O, Teitelbaum D, Arnon R 1977 Effect of a synthetic polypeptide (Cop 1) on patients with multiple sclerosis and acute disseminated encephalomyelitis: preliminary report. *J Neurol Sci* **31**: 433–438

Academy of Medical Sciences 2004 *Restoring Neurological Function: Putting the Neurosciences to Work in Neurorehabilitation*. London: Academy of Medical Sciences, p. 71

Acar G, Idiman F, Idiman E *et al* 2003 Nitric oxide as an activity marker in multiple sclerosis. *J Neurol* **250**: 588–592

Acarin N, Rio J, Fernandez AL *et al* 1996 Different antiganglioside antibody pattern between relapsing–remitting and progressive multiple sclerosis. *Acta Neurol Scand* **93**: 99–103

Acha-Orbea H, Mitchell DJ, Timmermann L *et al* 1988 Limited heterogeneity of T cell receptors from lymphocytes mediating autoimmune encephalomyelitis allows specific immune intervention. *Cell* **54**: 263–273

Acheson ED, Bachrach CA, Wright FM 1960 Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation and other variables. *Acta Neurol Scand* **35**: 132–47

Achiron A, Ziv A, Djaldetti R *et al* 1992a Aphasia in multiple sclerosis: clinical and radiologic correlations. *Neurology* **42**: 2195–2197

Achiron A, Pras E, Gilad R *et al* 1992b Open controlled therapeutic trial of intravenous immune globulin in relapsing–remitting multiple sclerosis. *Arch Neurol* **49**: 1233–1236

Achiron A, Gabbay U, Gilad R *et al* 1998 Intravenous immunoglobulin in multiple sclerosis: a double-blind, placebo-controlled trial. *Neurology* **50**: 398–402

Achiron A, Barak Y, Rotstein Z 2003 Longitudinal disability curves for predicting the course of relapsing–remitting multiple sclerosis. *Mult Scler* **9**: 486–491

Achiron A, Edelstein S, Viev-Ner Y *et al* 2004a Bone strength in multiple sclerosis: cortical midtibial speed-of-sound assessment. *Mult Scler* **10**: 488–493

Achiron A, Kishner I, Dolev M *et al* 2004b Effect of intravenous immunoglobulin treatment on pregnancy and postpartum-related relapses in multiple sclerosis. *J Neurol* **251**: 1133–1137

Achiron A, Polliack M, Rao SM *et al* 2005 Cognitive patterns and progression in multiple sclerosis: construction and validation of percentile curves. *J Neurol Neurosurg Psychiatry* **76**: 744–749

Ackerman KD, Heyman R, Rabin BS *et al* 2002 Stressful life events precede exacerbations of multiple sclerosis. *Psychosom Med* **64**: 916–920

Ackerman KD, Stover A, Heyman R *et al* 2003 Relationship of cardiovascular reactivity, stressful life events, and multiple sclerosis disease activity. *Brain Behav Immun* **17**: 141–151

Ackerman R, Rehse-Küpper B, Gollmer E, Schmidt R 1988 Chronic neurologic manifestations of erythema migrans borreliosis. *Ann NY Acad Sci* **539**: 16–23

ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature 1999 The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* **42**: 599–668

Adam AM 1989 Multiple sclerosis: epidemic in Kenya. *East Afr Med J* **66**: 503–506

Adams CW 1977 Pathology of multiple sclerosis: progression of the lesion. *Br Med Bull* **33**:15–20

Adams CW, Poston RN 1990 Macrophage histology in paraffin-embedded multiple sclerosis plaques is demonstrated by the monoclonal pan-macrophage marker HAM-56: correlation with chronicity of the lesion. *Acta Neuropathol* **80**: 208–211

Adams CW, Abdulla YH, Torres EM, Poston RN 1987 Periventricular lesions in multiple sclerosis: their perivenous origin and relationship to granular ependymitis. *Neuropathol Appl Neurobiol* **13**: 141–152

Adams CW, Poston RN, Buk SJ 1989 Pathology, histochemistry and immunocytochemistry of lesions in acute multiple sclerosis. *J Neurol Sci* **92**: 291–306

Adams DK, Sutherland JM, Fletcher WB 1950 Early clinical manifestations of disseminated sclerosis. *Br Med J* **2**: 431–436

Adams RD, Kubik CS 1952 The morbid anatomy of the demyelinating diseases. *Am J Med* **12**: 510–546

Adelman B, Sandrock A, Panzara MA 2005 Natalizumab and progressive multifocal leukoencephalopathy. *N Engl J Med* **353**: 432–433

Ader M, Schachner M, Bartsch U 2001 Transplantation of neural precursor cells into the dysmyelinated CNS of mutant mice deficient in the myelin-associated glycoprotein and Fyn tyrosine kinase. *Eur J Neurosci* **14**: 561–566

Adie WJ 1930 Acute retrobulbar neuritis in disseminated sclerosis. *Trans Ophthalmol Soc UK* **103**: 262–267

Afshar G, Muraro PA, McFarland HF, Martin R 1998 Lack of over-expression of T cell receptor Vβ5.2 in myelin basic protein-specific T cell lines derived from HLA-DR2 positive multiple sclerosis patients and controls. *J Neuroimmunol* **84**: 7–13

Agresti C, Bernardo A, Del Russo N *et al* 1998 Synergistic stimulation of MHC class I and IRF-1 gene expression by IFN-γ and TNF-α in oligodendrocytes. *Eur J Neurosci* **10**: 2975–2983

Agresti C, Meomartini ME, Amadio S *et al* 2005 ATP regulates oligodendrocyte progenitor migration, proliferation, and differentiation: involvement of metabotropic P2 receptors. *Brain Res Rev* **48**: 157–165

Agundez JAG, Arroyo R, Ledesma MC *et al* 1995 Frequency of CYP2D6 allelic variants in multiple sclerosis. *Acta Neurol Scand* **92**: 464–467

Aharoni R, Teitelbaum D, Sela M, Arnon R 1997 Copolymer 1 induces T cells of the T helper type 2 that crossreact with myelin basic protein and suppress experimental autoimmune encephalomyelitis. *Proc Natl Acad Sci USA* **94**: 10821–10826

Aharoni R, Teitelbaum D, Sela M, Arnon R 1998 Bystander suppression of experimental autoimmune encephalomyelitis by T cell lines and clones of the Th2 type induced by copolymer 1. *J Neuroimmunol* **91**: 135–146

Aharoni R, Kayhan B, Eilam R *et al* 2003 Glatiramer acetate-specific T cells in the brain express T helper 2/3 cytokines and brain-derived neurotrophic factor *in situ*. *Proc Natl Acad Sci USA* **100**: 14157–14162

Ahern GP, Hsu S-F, Jackson MB 1999 Direct actions of nitric oxide on rat neurohypophysial K+ channels. *J Physiol* **520**: 165–176

Ahern GP, Hsu S-F, Klyachko VA, Jackson MB 2000 Induction of persistent sodium current by exogenous and endogenous nitric oxide. *J Biol Chem* **275**: 28810–28815

Ahlgren C, Anderson O 2005 No major birth order effect on the risk of multiple sclerosis. *Neuroepidemiology* **24**: 38–41

Ahmed I 1988 Survival after herpes simplex type II myelitis. *Neurology* **38**: 1500

Aisen M, Arlt G, Foster S 1990 Diaphragmatic paralysis without bulbar or limb paralysis in multiple sclerosis. *Chest* **98**: 499–501

Aisen ML, Arnold A, Baiges I, Maxwell S, Rosen M 1993 The effect of mechanical damping loads on disabling action tremor. *Neurology* **43**: 1346–1350

Aisen M, Sevilla D, Fox N 1996 Inpatient rehabilitation for multiple sclerosis. *J Neurol Rehab* **10**: 43–46

Akassoglou K, Bauer J, Kassiotis G *et al* 1998 Oligodendrocyte apoptosis and primary demyelination induced by local TNF/p55TNF receptor signaling in the central nervous system of transgenic mice: models for multiple sclerosis with primary oligodendrogliopathy. *Am J Pathol* **153**: 801–813

Akassoglou K, Douni E, Bauer J *et al* 2003 Exclusive tumor necrosis factor (TNF) signaling by the p75TNF receptor triggers inflammatory ischemia in the CNS of transgenic mice. *Proc Natl Acad Sci USA* **100**: 709–714

Akassoglou K, Adams RA, Bauer J *et al* 2004 Fibrin depletion decreases inflammation and delays the onset of demyelination in a tumor necrosis factor transgenic mouse model for multiple sclerosis. *Proc Natl Acad Sci USA* **101**: 6698–6703

Akenami FO, Siren V, Koskiniemi M, Siimes MA, Teravainen H, Vaheri A 1996 Cerebrospinal fluid activity of tissue plasminogen activator in patients with neurological diseases. *J Clin Pathol* **49**: 577–580

Åkesson E, Oturai A, Berg J *et al* 2002 A genome-wide screen for linkage in Nordic sib-pairs with multiple sclerosis. *Genes Immun* **3**: 279–285

Åkesson E, Coraddu F, Marrosu M *et al* 2003 Refining the linkage analysis on chromosome 10 in 449 sib-pairs with multiple sclerosis. *J Neuroimmunol* **143**: 31–38

Akira S, Takeda K, Kaisho T 2001 Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol 2*: 675–680

Akiyama Y, Honmou O, Kato T *et al* 2001 Transplantation of clonal neural precursor cells derived from adult human brain established functional peripheral myelin in the rat spinal cord. *Exp Neurol* **167**: 27–39

Akiyama Y, Radtke C, Kocsis JD 2002 Remyelination of the rat spinal cord by transplantation of identified bone marrow stromal cells. *J Neurosci* **22**: 6623–6630

Akman-Demir G, Bahar S, Coban O *et al* 2003 Cranial MRI in Behcet's disease: 134 examinations of 98 patients. *Neuroradiology* **45**: 851–859

Alajouanine T, Thurel T, Papaioanou C 1949 La douleur à type de décharge électrique provoquée par la flexion de la tête et parcourant le corps de haut en bas. *Rev Neurol* **81**: 89–97

Alam SM, Kyriakides T, Lawden M, Newman PK 1993 Methylprednisolone in multiple sclerosis: a comparison of oral with intravenous therapy at equivalent high dose. *J Neurol Neurosurg Psychiatry* **56**: 1219–1220

Albani C, Albani G 1997 A case of cutaneous necrosis during interferon-β 1b (β-IFN) therapy in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **62**: 418–428

Albers JW, Kelly JJ 1989 Acquired inflammatory demyelinating polyneuropathies: clinical and electrodiagnostic features. *Muscle Nerve* **12**: 435–451

Albina JE, Henry WL Jr 1991 Suppression of lymphocyte proliferation through the nitric oxide synthesizing pathway. *J Surg Res* **50**: 403–409

Albrecht PJ, Murtie JC, Ness JK *et al* 2003 Astrocytes produce CNTF during the remyelination phase of viral-induced spinal cord demyelination to stimulate FGF-2 production. *Neurobiol Dis* **13**: 89–101

Al Deeb SM, Yaqub BA, Bruyn GW, Biary NM 1997 Acute transverse myelitis. A localized form of postinfectious encephalomyelitis. *Brain* **120**: 115–1122

Alderton WK, Cooper CE, Knowles RG 2001 Nitric oxide synthases: structure, function and inhibition. *Biochem J* **357**: 593–615

Al-Din ASN 1986 Multiple sclerosis in Kuwait: clinical and epidemiological study. *J Neurol Neurosurg Psychiatry* **49**: 928–931

Al-Din ASN, Al-Saffar M, Siboo R, Behbehani K 1986 Association between HLA-D region epitopes and multiple sclerosis. *Tissue Antigens* **27**: 196–200

Al-Din ASN, Khogali M, Poser CM *et al* 1990 Epidemiology of multiple sclerosis in Arabs in Kuwait: a comparative study between Kuwaitis and Palestinians. *J Neurol Sci* **100**: 137–141

Aladro Y, Alemany MJ, Perez-Vieitez MC *et al* 2005 Prevalence and incidence of multiple sclerosis in Las Palmas, Canary Islands, Spain. *Neuroepidemiology* **24**: 70–75

Al-Araji A, Mohammed AI 2005 Multiple sclerosis in Iraq: does it have the same features encountered in Western countries? *J Neurol Sci* **234**: 67–71

Al-Araji AH, Oger J 2005 Reappraisal of Lhermitte's sign in multiple sclerosis. *Mult Scler* **11**: 398–402

Alehan FK, Kahveci S, Uslu Y *et al* 2004 Acute disseminated encephalomyelitis associated with hepatitis A virus infection. *Ann Trop Paediatr* **24**: 141–144

Alessandri-Haber N, Paillart C, Arsac C *et al* 1999 Specific distribution of sodium channels in axons of rat embryo spinal motoneurones. *J Physiol* **518**: 203–214

Alexander EL, Malinow K, Lejewski JE, Jerdan ME, Provost TT, Alexander GE 1986 Primary Sjögren's syndrome with central nervous system disease mimicking multiple sclerosis. *Ann Intern Med* **104**: 323–330

Alexander L, Loman J, Lesses HF, Green I 1950 Blood groups and multiple sclerosis. *Assoc Res Nerv Ment Disease* **28**: 179–200

Alexander WS 2002 Suppressors of cytokine signalling (SOCS) in the immune system. *Nature Rev Immunol 2*: 410–416

Alizadeh M, Babron M-C, Birebent B *et al* 2003a Genetic interaction of CTLA-4 with HLA-DR15 in multiple sclerosis patients. *Ann Neurol* **54**: 119–122

Alizadeh M, Génin E, Babron MC *et al* 2003b Genetic analysis of multiple sclerosis in Europeans: French data. *J Neuroimmunol* **143**: 74–78

Allarmargot C, Pouplard-Barthelaix A, Fressinaud C 2001 A single intracerebral microinjection of platelet-derived growth factor (PDGF) accelerates the rate of remyelination in vivo. *Brain Res* **918**: 28–39

Allbutt TC 1871 *On the Use of the Ophthalmoscope in Disease of the Nervous*

System and the Kidneys. London: Macmillan

Allcock RJ, de la Concha EG, Fernandez-Arguero M *et al* 1999 Susceptibility to multiple sclerosis mediated by HLA-DRB1 is influenced by a second gene telomeric of the TNF cluster. *Hum Immunol* **60**: 1266–1273

Allegretta M, Nicklas JA, Sriram S, Albertini RJ 1990 T cells responsive to myelin basic protein in patients with multiple sclerosis. *Science* **247**: 718–721

Allen IV 1991 Pathology of multiple sclerosis. In: Matthews WB (ed.) *McAlpine's Multiple Sclerosis*, 2nd edn. Edinburgh: Churchill Livingstone, pp. 341–378

Allen IV, Millar JH, Hutchinson MJ 1978 General disease in 120 necropsy-proven cases of multiple sclerosis. *Neuropathol Appl Neurobiol* **4**: 279–284

Allen IV, Glover G, McKeown SR, McCormick D 1979 The cellular origin of lysosomal enzymes in the plaque in multiple sclerosis. A histochemical study with combined demonstration of myelin and acid phosphatase. *Neuropathol Appl Neurobiol* **5**: 197–210

Allen IV, Glover G, Anderson R 1981 Abnormalities in the macroscopically normal white matter in cases of mild or spinal multiple sclerosis (MS). *Acta Neuropathol* **7 (Suppl)**: 176–178

Allen IV, McQuid S, Miradkhur M, Nevin G 2001 Pathological abnormalities in the normal-appearing white matter in multiple sclerosis. *Neurol Sci* **22**:141–144

Allen KW 1994 The prevalence of multiple sclerosis in the health district of Bassetlaw. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 104–112

Allen M, Sandberg-Wollheim M, Sjogren K *et al* 1994 Association of susceptibility to multiple sclerosis in Sweden with HLA class II DRB1 and DQB1 alleles. *Hum Immunol* **39**: 41–48

Allen RK, Sellars RE, Sandstrom PA 2003 A prospective study of 32 patients with neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* **20**: 149–151

Allison RS 1931 Disseminated sclerosis in North Wales: an inquiry into its incidence, frequency, distribution and other etiological factors. *Brain* **53**: 391–430

Allison RS 1943 *Sea Diseases*. London: Bale

Allison RS 1950 Survival in disseminated sclerosis: a clinical study of a series of cases first seen twenty years ago. *Brain* **73**: 103–120

Allison RS 1963 Some neurologic aspects of medical geography. *Proc R Soc Med* **56**: 71–76

Allison RS, Millar JHD 1954 Prevalence and familial incidence of disseminated sclerosis (a report to the Northern Ireland Hospitals Authority on the results of a three year survey). Prevalence of disseminated sclerosis in Northern Ireland. *Ulster Med J* **23 (Suppl 2)**: 91

Allison TJ, Garboczi DN 2002 Structure of γδ T cell receptors and their recognition of non-peptide antigens. *Mol Immunol* **38**: 1051–1061

Almazan G, Liu HN, Khorchid A *et al* 2000 Exposure of developing oligodendrocytes to cadmium causes HSP72 induction, free radical generation, reduction of glutathione levels, and cell death. *Free Radic Biol Med* **29**: 858–869

Almeras L, Meresse B, Seze J *et al* 2002 Interleukin-10 promoter polymorphism in multiple sclerosis: association with disease progression. *Eur Cytokine Netw* **13**: 200–206

Aloisi F, Giampaolo A, Russo G *et al* 1992 Developmental appearance, antigenic profile and proliferation of glial cells of the human embryonic spinal cord. *Glia* **5**: 171–181

Alonso G 2000 Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. *Glia* **31**: 219–231

Alonso-Valle H, Munoz R, Hernandez JL, Matorras P 2001 Acute disseminated encephalomyelitis following *Leptospira* infection. *Eur Neurol* **46**:104–105

Alotaibi S, Kennedy J, Tellier R *et al* 2004 Epstein–Barr virus in pediatric multiple sclerosis. *J Am Med Assoc* **291**: 1875–1879

Alperovitch A, LaCanuet P, Marteau R 1981 Birth order and risk of multiple sclerosis: are they associated and how? *Acta Neurol Scand* **63**: 136–138

Alpini D, Pugnetti L, Caputo D *et al* 2004 Vestibular evoked myogenic potentials in multiple sclerosis: clinical and imaging correlations. *Mult Scler* **10**: 316–321

Alsalameh S, Manger B, Kern P, Kalden J 1998 New onset of rheumatoid arthritis during interferon beta-1b treatment in a patient with multiple sclerosis: comment on the case report by Jabaily and Thompson. *Arthritis Rheum* **41**: 754

Al-Shammri S, Nelson RF, Voevodin A 2003 HHV-6 DNAemia in patients with multiple sclerosis in Kuwait. *Acta Neurol Scand* **107**: 122–124

Al-Shammri S, Nelson RF, Al-Muzairi I, Akanji AO 2004 HLA determinants of susceptibility to multiple sclerosis in an Arabian Gulf population. *Mult Scler* **10**: 381–386

Alshubaili AF, Alramzy K, Ayyad, YM, Gerish Y 2005 Epidemiology of multiple sclerosis in Kuwait: new trends in incidence and prevalence. *Eur Neurol* **53**: 125–131

Alter M, Speer J 1968 Clinical evaluation of possible etiologic factors in multiple sclerosis. *Neurology* **18**: 109–115

Alter M, Halpern L, Kurland LT *et al* 1962 Multiple sclerosis in Israel: prevalence among immigrants and native inhabitants. *Arch Neurol* **7**: 253–263

Alter M, Okihiro M, Rowley W, Morris T 1971 Multiple sclerosis among orientals and caucasians in Hawaii. *Neurology* **21**: 122–130

Alter M, Harshe M, Anderson E *et al* 1976 Genetic association of multiple sclerosis and HLA determinants. *Neurology* **26**: 31–36

Alter M, Kahana E, Loewenson R 1978 Migration and risk of multiple sclerosis. *Neurology* **28**: 1089–1093

Althaus HH, Kloppner S, Schmidt-Schultz T, Schwartz P 1992 Nerve growth factor induces proliferation and enhances fiber regeneration in oligodendrocytes isolated from adult pig brain. *Neurosci Lett* **135**: 219–223

Althaus J 1877 *Diseases of the Nervous System*. London: Smith Elder & Co, pp. 330–335

Altintas A, Cai Z, Pease LR, Rodriguez M 1993 Differential expression of H-2K and H-2D in the central nervous system of mice infected with Theiler's virus. *J. Immunol* **151**: 2803–2812

Altintas A, Alici Y, Melikoglu M, Siva A 2002 Arthritis during interferon beta-1b treatment in multiple sclerosis. *Mult Scler* **8**: 534–536

Altrocchi PH 1963 Acute transverse myelopathy. *Arch Neurol* **9**: 111–119

Alusi SH, Glickman S, Aziz TZ, Bain PG 1999 Tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **66**: 131–134

Alusi SH, Worthington J, Glickman S, Bain PG 2001a A study of tremor in multiple sclerosis. *Brain* **124**: 720–730

Alusi SH, Aziz TZ, Glickman S *et al* 2001b Stereotactic lesional surgery for the treatment of tremor in multiple sclerosis: a prospective case-controlled study. *Brain* **124**: 1576–1589

Alvarado-de la Barrera C, Zuniga-Ramos J *et al* 2000 HLA class II genotypes in Mexican Mestizos with familial and non-familial multiple sclerosis. *Neurology* **55**: 1897–1900

Alvarez G, Castillo JL, Ruiz F *et al* 1992 Multiple sclerosis in Chile. *Acta Neurol Scand* **85**: 1–4

Alvarez-Dolado M, Pardal R, Garcia-Verdugo JM *et al* 2003 Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes. *Nature* **425**: 968–973

Alves D, Pires MM, Guimarès A, Miranda MC 1986 Four cases of late onset metachromatic leukodystrophy in a family: clinical, biochemical and neuropathological studies. *J Neurol Neurosurg Psychiatry* **49**: 1417–1422

Alvord EC 1985 Disseminated encephalomyelitis: its variations in form and their relationships to other diseases of the nervous system. In: Koetsier JC (ed.) *Handbook of Clinical Neurology*, Vol 47. Amsterdam: Elsevier, pp. 467–502

Alvord EC, Kies MW 1959 Clinico-pathological correlations in experimental allergic encephalomyelitis II Development of an index for quantitative assay of encephalitogenic activity of antigens. *J Neuropath Exp Neurol* **18**: 447–457

Alvord EC, Shaw CM, Hruby S, Kies MW 1965 Encephalitogen-induced inhibition of experimental allergic encephalomyelitis: prevention, suppression and therapy. *Ann NY Acad Sci* **122**: 333–345

Amato MP, Ponziani G 2000 A prospective study on the prognosis of multiple sclerosis. *Neurol Sci* **21 (Suppl)**: 831–838

Amato MP, Fratiglioni L, Groppi C *et al* 1988 Interrater reliability in assessing functional systems and disability on Kurtzke scale in multiple sclerosis. *Arch Neurol* **45**: 746–748

Amato MP, Pracucci G, Ponziano G *et al* 1993 Long term safety of azathioprine therapy in multiple sclerosis. *Neurology* **43**: 831–833

Amato MP, Ponziani G, Pracucci G *et al* 1995 Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. *Arch Neurol* **52**: 168–172

Amato MP, Ponziani G, Bartolozzi ML, Siracusa G 1999 A prospective study on the natural history of multiple sclerosis: clues to the conduct and interpretation of clinical trials. *J Neurol Sci* **168**: 96–106

Amato MP, Ponziani G, Siracusa G, Sorbi S 2001 Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Arch Neurol* **58**: 1602–1606

Amato MP, Battaglia MA, Caputo D *et al* 2002 The costs of multiple sclerosis: a cross-sectional, multicenter cost-of-illness study in Italy. *J Neurol* **249**: 152–163

Amato MP, Grimaud J, Achiti I *et al* 2004 European validation of a standardized clinical description of multiple sclerosis. *J Neurol* **251**: 1472–1480

Ambrosini E, Columba-Cabezas S, Serafini B *et al* 2003 Astrocytes are the major intracerebral source of macrophage inflammatory protein-3alpha/CCL20 in relapsing experimental autoimmune encephalomyelitis and in vitro. *Glia* **41**: 290–300

Amela-Peris R, Aladro Y, Conde-Sendin MA *et al* 2004 Familial multiple sclerosis in Canary Islands. *Rev Neurol* **39**: 911–914

American PVO 1999 *Multiple Sclerosis Clinical Practice Guidelines: Fatigue And Multiple Sclerosis – evidence-based management strategies for fatigue in multiple sclerosis*. Washington, DC: Paralyzed Veterans of America

Ames FR, Louw S 1977 Multiple sclerosis in coloured South Africans. *J Neurol Neurosurg Psychiatry* **40**: 729–735

Aminoff MJ, Logue V 1974 Clinical features of spinal vascular malformations. *Brain* **97**: 197–210

Amirzargar A, Mytilineos J, Yousefipour A *et al* 1998 HLA class II (DRB1, DQA1 and DQB1) associated genetic susceptibility in Iranian multiple sclerosis (MS) patients. *Eur J Immunogenet* **25**: 297–301

Amor S, Groome N, Linington C *et al* 1994 Identification of epitopes of myelin oligodendrocyte glycoprotein for the induction of experimental allergic encephalomyelitis in SJL and Biozzi AB/H mice. *J Immunol* **153**: 4349–4356

An SF, Groves M, Martinian L *et al* 2002 Detection of infectious agents in brain of patients with acute hemorrhagic leukoencephalitis. *J Neurovirol* **8**: 439–446

Andermann F, Cosgrove JBR, Lloyd-Smith D, Walters AM 1959 Paroxysmal dysarthria and ataxia in multiple sclerosis. A report of two unusual cases. *Neurology* **9**: 211–216

Andermann F, Cosgrove JBR, Lloyd-Smith DL *et al* 1961 Facial myokymia in multiple sclerosis. *Brain* **84**: 31–44

Andersen O, Lygner P-E, Bergstrom T *et al* 1993 Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. *J Neurol* **240**: 417–422

Andersen O, Lycke J, Tollesson PO *et al* 1996 Linomide reduces the rate of active lesions in relapsing–remitting multiple sclerosis. *Neurology* **47**: 895–900

Anderson AC, Nicholson LB, Legge KL *et al* 2000 High frequency of autoreactive myelin proteolipid protein-specific T cells in the periphery of naive mice: mechanisms of selection of the self-reactive repertoire. *J Exp Med* **191**: 761–770

Anderson CM, Nedergaard M 2003 Astrocyte-mediated control of cerebral microcirculation. *Trends Neurosci* **26**: 340–344

Anderson DW, Ellenberg JH, Leventhal CM *et al* 1992 Revised estimate of the prevalence of multiple sclerosis in the United States. *Ann Neurol* **31**: 333–336

Anderson MS, Venanzi ES, Klein L *et al* 2002 Projection of an immunological self shadow within the thymus by the AIRE protein. *Science* **298**: 1395–1401

Anderson SA, Shukaliak-Quandt J, Jordan EK *et al* 2004 Magnetic resonance imaging of labelled T-cells in a mouse model of multiple sclerosis. *Ann Neurol* **55**: 654–659

Anderson UG, Bjork L, Skansen-Saphir U, Anderson JP 1993 Down-regulation of cytokine production and interleukin-2 receptor expression by pooled human IgG. *Immunology* **79**: 211–216

Andersson M, Alvarez-Cermeno J, Bernardi G *et al* 1994 Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. *J Neurol Neurosurg Psychiatry* **57**: 897–902

Andersson PB, Perry VH, Gordon S 1992 The acute inflammatory response to lipopolysaccharide in CNS parenchyma differs from that in other body tissues. *Neuroscience* **48**: 169–186

Andersson PB, Waubant E, Gee L, Goodkin DE 1999 Multiple sclerosis that is progressive from the time of onset. Clinical characteristics and progression of disability. *Arch Neurol* **56**: 1138–1142

Andjelkovic AV, Pachter JS 1998 Central nervous system endothelium in neuroinflammatory, neuroinfectious, and neurodegenerative disease. *J Neurosci Res* **51**: 423–430

Andler W, Roosen K 1980 Multiple Sklerose im ersten Lebensjahrzehnt. *Klin Pädiatr* **192**: 365–369

Ando DG, Clayton J, Kono D *et al* 1989 Encephalitogenic T cells in the B10.PL model of experimental allergic encephalomyelitis (EAE) are of the Th1 lymphokine subtype cell. *Immunology* **124**: 132–143

de Andres C, Guillem A, Rodriguez-Mahou M, Lopez Longo FJ 2001 Frequency and significance of anti-Ro (SS-A) antibodies in multiple sclerosis patients. *Acta Neurol Scand* **104**: 83–87

Andrews JM 1972 The ultrastructural neuropathology of multiple sclerosis. In: Wolfgram F, Ellison GW, Stevens JG (eds) *Multiple Sclerosis. Immunology, Virology and Ultrastructure*. New York: Academic Press, pp. 23–52

Andrews KL, Husmann DA 1997 Bladder dysfunction and management in multiple sclerosis. *Mayo Clin Proc* **72**: 1176–1183

von Andrian UH, Engelhardt B 2003 Alpha4 integrins as therapeutic targets in autoimmune disease. *N Engl J Med* **348**: 68–72

von Andrian UH, Mackay CR 2000 T cell function and migration: two sides of the same coin. *N Engl J Med* **343**: 1020–1034

Andrianokos AA, Duffy J, Suzuki M, Sharp JT 1976 Transverse myelopathy in systemic lupus erythematosus. Report of three cases and review of literature. *Ann Intern Med* **83**: 616–624

Andriezen WL 1893 The neuroglial elements of the brain. *Br Med J* **2**: 227–230

Anema JR, Heijenbrok MW, Faes TJC *et al* 1991 Cardiovascular autonomic function in multiple sclerosis. *J Neurol Sci* **104**: 129–134

Annunziata P, D'Ettorre M, Menchini U *et al* 1988 Frequency of blood–retina and blood–brain barrier changes in multiple sclerosis. *Ital J Neurol Sci* **9**: 345–349

Annunziata P, Morana P, Giorgio A *et al* 2003 High frequency psoriasis in relatives is associated with early onset in an Italian multiple sclerosis cohort. *Acta Neurol Scand* **108**: 327–331

Annunziata P, Marroni M, Francisci D, Stagni G 2005 Acute transverse myelitis and hepatitis C virus. *Infez Med* **13**: 45–47

Anon 1873 Guys' Hospital. Case of insular sclerosis of the brain and spinal cord (under the care of Dr Moxon). *Lancet* **i**: 236

Anon 1875a Guys' Hospital. Two cases of insular sclerosis of the brain and spinal cord. *Lancet* **i**: 471–473

Anon 1875b Guys' Hospital. Two cases of insular sclerosis of the brain and spinal cord. *Lancet* **i**: 609

Anon 1875c Report on Clinical Society of London. *Lancet* **i**: 545

Anon 1948 Streptomycin treatment of pulmonary tuberculosis. A Medical Research Council investigation. *Br Med J* **ii**: 769–782

Anon 1950 Die multiple Sklerose des Menschen (book review). *Arch Neurol Psychiatry* **63**: 190

Anon 1992 Diagnosis of Sjögren's syndrome. *Lancet* **340**: 150–151

Anon 1994 Biogen's IFN-β-1a reduces progression of disability in multiple sclerosis. *Clin Courier* **12**: 1–4

Anon 1995 *Morbidity Statistics from General Practice. Fourth National Study 1991–2*,

OPCS series MB5 no. 3. London: HMSO (full version available in electronic format)
Anon 1998 Burden of illness of multiple sclerosis. Part I: Cost of illness. The Canadian Burden of Illness Study Group. *Can J Neurol Sci* **25**: 23–30
Ansari KA 1976 Olfaction in multiple sclerosis. *Eur Neurol* **14**: 138–145
Antel JP, Arnason BGW, Medof ME 1979 Suppressor cell function in multiple sclerosis: correlation with clinical disease severity. *Ann Neurol* **5**: 338–342
Antel JP, Reder AT, Noronha AB 1985 Cellular immunity and immune regulation in multiple sclerosis. *Semin Hematol* **5**: 117–126
Anthony DC, Ferguson B, Matyzak MK *et al* 1997 Differential matrix and metalloproteinase expression in cases of multiple sclerosis and stroke. *Neuropathol Appl Neurobiol* **23**: 406–415
Anthony DC, Miller KM, Fearn S *et al* 1998 Matrix metalloproteinase expression in an experimentally induced DTH model of multiple sclerosis. *J Neuroimmunol* **87**: 62–72
Antonovsky A, Leibowitz U, Medalie JM *et al* 1968 Reappraisal of possible etiologic factors in multiple sclerosis. *Am J Pub Health* **58**: 836–848
Antony JM, van Marle G, Opii W *et al* 2004 Human endogenous retrospective glycoprotein-mediated induction of redox reactants causes oligodendrocyte death and demyelination. *Nat Neurosci* **7**: 1021–1023
Appay V, Rowland-Jones SL 2002 The assessment of antigen-specific CD8+ T cells through the combination of MHC class I tetramer and intracellular staining. *J Immunol Meth* **268**: 9–19
Apple D, Keinees K, Biehl JP 1978 The syndrome of inappropriate antidiuretic hormone secretion in multiple sclerosis. *Arch Int Med* **138**: 1713–1714
Appleby MW, Ramsdell F 2003 A forward-genetic approach for analysis of the immune system. *Nat Rev Immunol* **3**: 463–471
Araki I, Matsui M Ozawa K *et al* 2003 Relationship of bladder dysfunction to lesion site in multiple sclerosis. *J Urol* **169**: 1384–1387
Archelos JJ, Hartung HP 2000 Pathogenetic role of autoantibodies in neurological disease. *Trends Neurosci* **23**: 317–327
Archelos JJ, Trotter J, Previtali S *et al* 1998 Isolation and characterisation of an oligodendrocyte precursor-derived B-cell epitope in multiple sclerosis. *Ann Neurol* **43**: 15–24
Archelos JJ, Storch MK, Hartung HP 2000 The role of B cells and autoantibodies in multiple sclerosis. *Ann Neurol* **47**: 694–706
Archibald CJ, Wei X, Scott JN *et al* 2004 Posterior fossa lesion volume and slowed information processing in multiple sclerosis. *Brain* **127**: 1526–1534
Arcos-Burgos M, Palacio G, Sanchez JL *et al* 1999 Multiple sclerosis: association to HLA DQalpha in a tropical population. *Exp Clin Immunogenet* **16**: 131–138
Ardissone P, Rota E, Durelli L *et al* 2002 Effects of high doses of corticosteroids on bone metabolism. *J Endocrin Invest* **25**: 129–133
Arevalo-Martin A, Vela JM, Molina-Holgado E *et al* 2003 Therapeutic action of cannabinoids in a murine model of multiple sclerosis. *J Neurosci* **23**: 2511–2516
Ariga T, Miyatake T, Yu RK 2001 Recent studies on the roles of antiglycosphingolipids in the pathogenesis of neurological disorders. *J Neurosci Res* **65**: 363–370
Aring CD 1965 Observations on multiple sclerosis and conversion hysteria. *Brain* **88**: 663–674
Armstrong MA, McDonnell GV, Graham CA *et al* 1999 Relationship between tumour necrosis factor-alpha (TNFalpha) production and a specific multiple sclerosis (MS) associated TNF gene haplotype. *Mult Scler* **5**: 165–170
Armstrong RC, Dorn HH, Kufta CV *et al* 1992 Pre-oligodendrocytes from adult human CNS. *J Neurosci* **12**: 1538–1547
Armutlu K, Karabudak R, Nurlu G 2001 Physiotherapy approaches in the treatment of ataxic multiple sclerosis: a pilot study. *Neurorehab Neural Repair* **15**: 203–211
Arnason BGW, Davis FA, Dean G *et al* 1982 Round the World. *Lancet* **112**: 734
Arnason BGW, Dayal A, Qu ZX *et al* 1996 Mechanisms of action of interferon-beta in multiple sclerosis. *Springer Semin Immunopathol* **18**: 125–148
Arnason BGW, Jacobs G, Hanlon M *et al* 1999 TNF neutralization in MS – results of a randomized, placebo-controlled multicenter study. *Neurology* **53**: 457–465
Arnett HA, Mason J, Marino M *et al* 2001 TNF alpha promotes proliferation of oligodendrocyte progenitors and remyelination. *Nat Neurosci* **4**: 1116–1122
Arnett HA, Fancy SPJ, Alberta JA *et al* 2004 bHLH transcription factor Olig1 is required to repair demyelinated lesions in the CNS. *Science* **306**: 2111–2115
Arnold AC, Pepose JS, Hepler RS, Foos RY 1984 Retinal periphlebitis and retinitis in multiple sclerosis I. Pathological characteristics. *Ophthalmology* **91**: 255–261
Arnold AC, Baloh RW, Yee RD, Hepler RS 1990 Internuclear ophthalmoplegia in the Chiari type II malformation. *Neurology* **40**: 1850–1854
Arnold B, Schönrich G, Hämmerling GJ 1993 Multiple levels of peripheral tolerance. *Immunol Today* **14**: 12–14
Arnouts C 1959 La sclérose en plaques chez l'enfant: une observation anatomoclinique et une observation clinique nouvelle. *Acta Neurol Belg* **59**: 796–814
Arroyo EJ, Scherer SS 2000 On the molecular architecture of myelinated fibers *Histochem Cell Biol* **113**: 1–18
Arroyo EJ, Xu Y-T, Zhou L *et al* 1999 Myelinating Schwann cells determine the internodal localization of Kv1.1, Kv1.2, Kvbeta2, and Caspr. *J Neurocytol* **28**: 333–347
Arroyo EJ, Xu T, Grinspan J *et al* 2002 Genetic dysmyelination alters the molecular architecture of the nodal region. *J Neurosci* **22**: 1726–1737
Arruda WO, Scola RH, Teive HA, Werneck LC 2001 Multiple sclerosis: report on 200 cases from Curitiba, southern Brazil, and comparison with other Brazilian series. *Arq Neuropsiquiatr* **59**: 165–170
Arsenijevic Y, Weiss S, Schneider B, Aebischer P 2001 Insulin-like growth factor-I is necessary for neural stem cell proliferation and demonstrates distinct actions of epidermal growth factor and fibroblast growth factor-2. *J Neurosci* **21**: 7194–7202
Arvanitis DN, Wang H, Bagshaw RD *et al* 2004 Membrane-associated estrogen receptor and caveolin-1 are present in central nervous system myelin and oligodendrocyte plasma membranes. *J Neurosci Res* **75**: 603–613
Arya SC 2001 Acute disseminated encephalomyelitis associated with poliomyelitis vaccine. *Pediatr Neurol* **24**: 325
Asakura K, Rodriguez M 1998 A unique population of circulating autoantibodies promotes central nervous system remyelination. *Mult Scler* **4**: 217–221
Asakura K, Miller D, Murray K *et al* 1996 Monoclonal autoantibody SCH94.03, which promotes central nervous system remyelination, recognizes an antigen on the surface of oligodendrocytes. *J Neurosci Res* **43**: 273–281
Ascherio A, Munch M 2001 Epstein Barr virus and multiple sclerosis. *Epidemiology* **11**: 220–224
Ascherio A, Zhang SM, Hernan MA *et al* 2001 Hepatitis B vaccination and the risk of multiple sclerosis. *New Engl J Med* **344**: 327–332
Aschoff JC, Conrad B, Kornhuber HH 1974 Acquired pendular nystagmus with oscillopsia in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **37**: 570–577
Ashburner J, Friston K 2000 Voxel-based morphometry – the methods. *NeuroImage* **11**: 805–821
Ashworth B 1957 Chronic retrobulbar and chiasmal neuritis. *Br J Ophthalmol* **51**: 698–702
Asselman P, Chadwick DW, Marsden CD 1975 Visual evoked responses in the diagnosis and management of multiple sclerosis. *Brain* **98**: 261–282
van Assen S, Bosma F, Staals LME *et al* 2004 Acute disseminated encephalomyelitis associated with *Borrelia burgdorferi*. *J Neurol* **251**: 626–629
Attar A, Lemann M, Ferguson A *et al* 1999 Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. *Gut* **44**: 226–230
Atwood A, Poser C 1961 Neurologic complications of Sjögren's syndrome. *Neurology* **11**: 1034–1041

Au WY, Lie AK, Cheung RT *et al* 2002 Acute disseminated encephalomyelitis after para-influenza infection post bone marrow transplantation. *Leuk Lymphoma* **43**: 455–457

Aubourg P, Feil R, Guidoux S 1990 The red-green visual pigment gene region in adrenoleucodystrophy. *Am J Hum Genet* **46**: 459–469

Auer DP, Schumann EM, Kumpfel T *et al* 2000 Seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann Neurol* **47**: 276–277

Auff E, Budka H 1980 Immunohistologische Methoden in der Neuropathologie. In: Jellinger K (ed.) *Curr Topics Neuropathol Facult Wien* **6**: 21–29

Aulkemeyer P, Hausner G, Brinkmeier H *et al* 2000 The small sodium-channel blocking factor in the cerebrospinal fluid of multiple sclerosis patients is probably an oligopeptide. *J Neurol Sci* **172**: 49–54

AUSTIMS Research Group 1989 Interferon-α and transfer factor in the treatment of multiple sclerosis: a double blind, placebo-controlled trial. *J Neurol Neurosurg Psychiatry* **52**: 566–574

Austin SG, Zee CS, Waters C 1992 The role of magnetic resonance imaging in acute transverse myelitis. *Can J Neurol Sci* **19**: 508–511

Averbuch-Heller L, Steiner I, Abramsky O 1992 Neurological manifestations of progressive systemic sclerosis. *Arch Neurol* **49**: 1292–1295

Averbuch-Heller L, Stahl JS, Rottach KG, Leigh RJ 1995 Gabapentin as treatment of nystagmus. *Ann Neurol* **38**: 972

Averbuch-Heller L, Tusa RJ, Fuhry L *et al* 1997 A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. *Ann Neurol* **41**: 818–825

Avis SP, Pryse-Phillips WE 1995 Sudden death in multiple sclerosis associated with sun exposure: a report of two cases. *Can J Neurol Sci* **22**: 305–307

Axelson O, Landtblom AM, Flodin U 2001 Multiple sclerosis and ionizing radiation. *Neuroepidemiology* **20**: 175–178

Axtell RC, Webb MS, Barnum SR, Raman C 2004 Cutting edge: critical role for CD5 in experimental autoimmune encephalomyelitis: inhibition of engagement reverses disease in mice. *J Immunol* **173**: 2928–2932

Azouvi P, Mane M, Thiebaut JB *et al* 1996 Intrathecal baclofen administration for control of severe spinal spasticity: functional improvement and long-term follow-up. *Arch Phys Med Rehab* **77**: 35–39

Baas D, Legrand C, Samarut J, Flamant F 2002 Persistence of oligodendrocyte precursor cells and altered myelination in optic nerve associated to retina degeneration in mice devoid of all thyroid hormone receptors. *Proc Natl Acad Sci USA* **99**: 2907–2911

Baba H, Akita H, Ishibashi T *et al* 1999 Completion of myelin compaction, but not the attachment of oligodendroglial processes triggers K+ channel clustering. *J Neurosci Res* **58**: 752–764

Babbe H, Roers A, Waisman A *et al* 2000 Clonal expansion of CD8+ T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. *J Exp Med* **192**: 393–404

Babinski J 1885a *Étude anatomique et clinique sur la sclérose en plaques*. Paris: Masson

Babinski J 1885b Recherches sur l'anatomie pathologique de la sclérose en plaques et etude comparative des diverses varietes de la scléroses de la moelle. *Arch Physiol (Paris)* **2–6**:186–207

Babinski J, Dubois R 1918 Douleurs à forme décharge électrique consécutives aux traumatismes de la nuque. *Presse Méd* **26**: 64

Bach J-F 2003 Regulatory T cells under scrutiny. *Nat Rev Immunol* **3**: 189–198

Bachman DS, Laó-Velez C, Estanol B 1976 Dystonia and choreoathetosis in multiple sclerosis. *Arch Neurol* **33**: 590

Bachmann MF, Kopf M 2001 On the role of the innate immunity in autoimmune disease. *J Exp Med* **193**: F47–F50

Bachmann R, Eugster HP, Frei K *et al* 1999 Impairment of TNF-receptor 1 signalling but not Fas signalling diminishes T-cell apoptosis in MOG-peptide induced chronic demyelinating autoimmune encephalomyelitis in mice. *Am J Pathol* **154**: 1417–1422

Back SA, Luo NL, Borenstein NS *et al* 2002 Arrested oligodendrocyte lineage progression during human cerebral white matter development: dissociation between the timing of progenitor differentiation and myelinogenesis. *J Neuropathol Exp Neurol* **61**: 197–211

Bagasra O, Michaels FH, Zheng YM *et al* 1995 Activation of the inducible form of nitric oxide synthase in the brains of patients with multiple sclerosis. *Proc Natl Acad Sci USA* **92**: 12041–12045

Bagnato F, Jeffries N, Richert ND *et al* 2003 Evolution of T1 black holes in patients with multiple sclerosis imaged monthly for four years. *Brain* **126**: 1782–1789

Baig S, Olsson T, Yu-Ping J *et al* 1991 Multiple sclerosis: cells secreting antibodies against myelin-associated glycoprotein are present in the cerebrospinal fluid. *Scand J Immunol* **33**: 73–79

Bailey P 1950 Letter to the editor. *Arch Neurol Psychiatry* **63**: 790

Baillie 1820 Some observations upon paraplegia in adults. *Med Trans R Coll Phys Lond* **6**: 16–26

Bains JS, Ferguson AV 1997 Nitric oxide depolarizes type II paraventricular nucleus neurons in vitro. *Neuroscience* **79**: 149–159

Bajaj NP, Waldman A, Orrell R *et al* 2002 Familial adult onset of Krabbe's disease resembling hereditary spastic paraplegia with normal neuroimaging. *J Neurol Neurosurg Psychiatry* **72**: 635–638

Bajramovic JJ, Lassmann H, van-Noort JM 1997 Expression of alpha-β-crystallin in glia cells during lesional development in multiple sclerosis. *J Neuroimmunol* **78**: 143–151

Bakchine S, Duyckaerts Ch, Hassine L *et al* 1991 Lésions neurologiques centrales et périphériques au cours d'un syndrome de Gougerot-Sjögren primitif. *Rev Neurol* **147**: 368–375

Baker DG 2002 Multiple sclerosis and thermoregulatory dysfunction. *J Appl Physiol* **92**: 1779–1780

Baker D, Pryce G 2003 The therapeutic potential of cannabis in multiple sclerosis. *Expert Opin Invest Drugs* **12**: 561–567

Baker D, Rosenwasser OA, O'Neill JK, Turk JL 1995 Genetic analysis of experimental allergic encephalomyelitis in mice. *J Immunol* **155**: 4046–4051

Baker D, Adamson P, Greenwood J 2003 Potential of statins for the treatment of multiple sclerosis. *Lancet Neurol* **2**: 9–10

Baker JB, Larson SJ, Sances A, White PT 1968 Evoked potentials as an aid to the diagnosis of multiple sclerosis. *Neurology* **18**: 286

Baker MD 2000 Axonal flip-flops and oscillators. *Trends Neurosci* **23**: 514–519

Baker MD, Bostock H 1992 Ectopic activity in demyelinated spinal root axons of the rat. *J Physiol* **451**: 539–552

Baker MD, Bostock H 1999 The pH dependence of late sodium current in large sensory neurons. *Neuroscience* **92**: 1119–1130

Bakke A, Myhr KM, Gronning M, Nyland H 1996 Bladder, bowel and sexual dysfunction in patients with multiple sclerosis—a cohort study. *Scand J Urol Nephrol* **179**: 61–66

Bakshi R, Mazziotta JC 1996 Acute transverse myelitis after influenza vaccination: magnetic resonance imaging findings. *J Neuroimag* **6**: 248–250

Bakshi R, Kinkel PR, Mechtler LL *et al* 1998 Magnetic resonance imaging findings in 22 cases of myelitis: comparison between patients with and without multiple sclerosis. *Eur J Neurol* **5**: 35–48

Bakshi R, Miletich RS, Henschel K *et al* 1999 Fatigue in multiple sclerosis: cross-sectional correlation with brain MRI findings in 71 patients. *Neurology* **53**: 1151–1153

Bakshi R, Dmochowski J, Shaikh ZA, Jacobs L 2001 Gray matter T2 hypointensity is related to plaques and atrophy in the brains of multiple sclerosis patients. *J Neurol Sci* **185**: 19–26

Bakshi R, Benedict RHB, Bermel RA *et al* 2002 T2 hypointensity in the deep gray matter of patients with multiple sclerosis. *Arch Neurol* **59**: 62–68

Balashov KE, Olek MJ, Smith DR *et al* 1998 Seasonal variation of interferon-gamma production in progressive multiple sclerosis. *Ann Neurol* **44**: 824–828

Balashov KE, Rottman JB, Weiner HL, Hancock WW 1999 CCR5(+) and CXCR3(+) T cells are increased in multiple sclerosis and their ligands MIP-1alpha and IP-10 are

expressed in demyelinating brain lesions. *Proc Natl Acad Sci USA* **96**: 6873–6878
Ballerini C, Campani D, Rombola G *et al* 2000 Association of apolipoprotein E polymorphism to clinical heterogeneity of multiple sclerosis. *Neurosci Lett* **296**: 174–176
Ballerini C, Roasati E, Salvetti M *et al* 2002 Protein tyrosine phosphatase receptor-type C exon 4 gene mutation distribution in an Italian multiple sclerosis population. *Neurosci Lett* **328**: 325–327
Ballerini C, Guerini FR, Rombola G *et al* 2004 HLA-multiple sclerosis association in continental Italy and correlation with disease prevalence in Europe. *J Neuroimmunol* **150**: 178–185
Balo J 1928 Encephalitis periaxialis concentrica. *Arch Neurol* **19**: 242–264
Balomenos D, Balderas RS, Mulvany KP *et al* 1995 Incomplete T cell receptor Vb allelic exclusion and dual Vb-expressing cells. *J Immunol* **155**: 3308–3312
Bal-Price A, Brown GC 2001 Inflammatory neurodegeneration mediated by nitric oxide from activated glia-inhibiting neuronal respiration, causing glutamate release and excitotoxicity. *J Neurosci* **21**: 6480–6491
Bamford CR, Sibley W, Laguna JF 1978a Anesthesia in multiple sclerosis. *Can J Neurol Sci* **5**: 41–44
Bamford CR, Sibley WA, Laguna JF 1978b Swine influenza vaccination in patients with multiple sclerosis. *Arch Neurol* **35**: 242–243
Bamford CR, Ganley JP, Sibley WA, Laguna JF 1978c Uveitis, perivenous sheathing and multiple sclerosis. *Neurology* **28**: 119–124
Bamford CR, Smith MS, Sibley WA 1980 Horner's syndrome: an unusual manifestation of multiple sclerosis. *Can J Neurol Sci* **7**: 65–66
Bamford CR, Sibley WA, Thies C *et al* 1981 Trauma as an etiologic and aggravating factor in multiple sclerosis. *Neurology* **31**: 1229–1234
Bamford CR, Sibley WA, Thies C 1983 Seasonal variation of multiple sclerosis exacerbations in Arizona. *Neurology* **33**: 697–701
Bamji SX, Majdan M, Pozniak CD *et al* 1998 The p75 neurotrophin receptor mediates neuronal apoptosis and is essential for naturally occurring sympathetic neuron death. *J Cell Biol* **140**: 911–923
Bammer HG, Schaltenbrand G, Solcher H 1960 Zwillingsunter-suchungen bei Multipler Sklerose. *Dtsch Z Nervenheilk* **181**: 261–279
Bammer HG, Hofman A, Zick R 1965 Aderhautentzündungen bei Multipler Sklerose und die sogenannten Uveoenzephalomeningitis. *Dtsch Z Nervenheilk* **187**: 300–316
Ban M, Stewart GJ, Bennetts BH *et al* 2002 A genome screen for linkage in Australian sibling-pairs with multiple sclerosis. *Genes Immun* **3**: 464–469
Ban M, Sawcer SJ, Heard R *et al* 2003 A genome wide screen for linkage disequilibrium in Australian HLA-DRB1*1501 positive multiple sclerosis patients. *J Neuroimmunol* **143**: 60–64
Ban M, Maranian M, Yeo TW *et al* 2005 No evidence for association of the protein kinase C alpha gene with multiple sclerosis. *J Neurol* **252**: 619–620
Banati RB, Newcombe J, Gunn RN *et al* 2000 The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity. *Brain* **123**: 2321–2337
Bandini F, Castello E, Mazzella L *et al* 2001 Gabapentin but not vigabatrin is effective in the treatment of acquired nystagmus in multiple sclerosis: how valid is the GABAergic hypothesis? *J Neurol Neurosurg Psychiatry* **71**: 107–110
Bandini F, Beronio A, Ghiglione E *et al* 2004 The diagnostic value of vestibular evoked myogenic potentials in multiple sclerosis: a comparative study with MRI and visually evoked potentials. *J Neurol* **251**: 617–621
Banerji NK, Millar JHD 1974 Chiari malformation presenting in adult life. *Brain* **97**: 157–168
Bangham CRM, Nightingale S, Cruickshank JK, Daenke S 1989 PCR analysis from multiple sclerosis patients for the presence of HTLV-1. *Science* **246**: 821
Banik NL 1992 Pathogenesis of myelin breakdown in demyelinating diseases: role of proteolytic enzymes. *Crit Rev Neurobiol* **6**: 257–271
Banik NL, Mauldin LB, Hogan EL 1979 Activity of 2′,3′-cyclic nucleotide 3′-phosphorylase in human cerebrospinal fluid. *Ann Neurol* **5**: 539–541
Bansal R, Pfeiffer SE 1997 FGF-2 converts mature oligodendrocytes to a novel phenotype. *J Neurosci Res* **50**: 215–228
Bansal A, van den Boom D, Kammerer S *et al* 2002 Association testing by DNA pooling: an effective initial screen. *Proc Natl Acad Sci USA* **99**: 16871–16874
Banwell B, Tremlett H 2005 Coming of age: the use of immunomodulatory therapy in children with multiple sclerosis. *Neurology* **64**: 778–779
Baoxun Z, Xuiqin I, Yupu G *et al* 1981 Multiple sclerosis: a clinical study from Beijing, China. *Eur Neurol* **20**: 394–400
Baranano DE, Ferris CD, Snyder SH 2001 Atypical neural messengers. *Trends Neurosci* **24**: 99–106
Baranzini SE, Jeong MC, Butunoi C *et al* 1999 B cell repertoire diversity and clonal expansion in multiple sclerosis brain lesions. *J Immunol* **163**: 5133–5144
Barbellion WNP 1919 *The Journal of a Disappointed Man*. London: Chatto & Windus
Barcellos LF, Klitz W, Field LL *et al* 1997a Association mapping of disease loci using a pooled DNA genomic screen. *Am J Hum Gen* **61**: 734–747
Barcellos LF, Thomson G, Carrington M *et al* 1997b Chromosome 19 single-locus and multilocus haplotype associations with multiple sclerosis. evidence of a new susceptibility locus in Caucasian and Chinese patients. *J Am Med Assoc* **278**: 1256–1261
Barcellos LF, Schito AM, Rimmler JB *et al* 2000 Chemokine receptor Δ5 polymorphism and age of onset in familial multiple sclerosis. Multiple Sclerosis Genetics Group. *Immunogenetics* **51**: 281–288
Barcellos LF, Caillier S, Dragone L *et al* 2001 PTPRC (CD45) is not associated with the development of multiple sclerosis in US patients. *Nature Genet* **29**: 23–24
Barcellos LF, Oksenberg JR, Green AJ *et al* 2002 Genetic basis for clinical expression in multiple sclerosis. *Brain* **125**: 150–158
Barcellos LF, Oksenberg JR, Begovich AB *et al* 2003 HLA-DR2 dose effect on susceptibility to multiple sclerosis and influence on disease course. *Am J Hum Genet* **72**: 710–716
Barcellos LF, Begovich AB, Reynolds RL *et al* 2004 Linkage and association with the NOS2A locus on chromosome 17q11 in multiple sclerosis. *Ann Neurol* **55**: 793–800
Baretz RM, Stephenson GR 1981 Emotional responses to multiple sclerosis. *Psychosoms* **22**: 117–127
Barger SW, Hörster D, Furukawa K *et al* 1995 Tumor necrosis factors a and b protect neurons against amyloid b-peptide toxicity: Evidence for involvement of a kB-binding factor and attenuation of peroxide and Ca^{2+} accumulation. *Proc Natl Acad Sci USA* **92**: 9328–9332
Bari F, Errico RA, Louis TM, Busija DW 1996 Interaction between ATP-sensitive K+ channels and nitric oxide on pial arterioles in piglets. *J Cereb Blood Flow Metab* **16**: 1158–1164
Barile L, Lavalle C 1992 Transverse myelitis in systemic lupus erythematosus: the effect of IV pulse methylprednisolone and cyclophosphamide. *J Rheumatol* **19**: 370–372
Barker AT, Jalinous R, Freeeston IL 1985 Non-invasive magnetic stimulation of the human motor cortex. *Lancet* **i**: 1106–1107
Barker AT, Freeston IL, Jalinous R, Jarratt JA 1986 Clinical evaluation of conduction time measurement in central motor pathways using magnetic stimulation of the human brain. *Lancet* **i**: 1325–1326
Barker CF, Billingham RE 1977 Immunologically privileged sites. *Adv Immunol* **25**: 1–54
Barker LF 1922 Exogenous causes of multiple sclerosis. In: *Multiple Sclerosis* [*Disseminated Sclerosis*]. New York: P.B. Hoeber and the Association for Research in Nervous and Mental Diseases, pp. 22–26, 48
Barkhof F, Polman C 1997 Oral or intravenous methylprednisolone for acute relapses of MS? *Lancet* **349**: 893–894
Barkhof F, Hommes OR, Scheltens P, Valk J 1991 Quantitative MRI changes in gadolinium-DPTA enhancement after high-dose intravenous methylprednisolone in multiple sclerosis. *Neurology* **41**: 1219–1222

Barkhof F, Freguin STFM, Hommes OR *et al* 1992 A correlative triad of gadolinium-DTPA MRI, EDSS and CSF-MBP in relapsing multiple sclerosis patients treated with high dose intravenous methylprednsiolone. *Neurology* **42**: 63–67

Barkhof F, Tas MW, Frequin ST *et al* 1994 Limited duration of the effect of methylprednsiolone on changes on MRI in multiple sclerosis. *Neuroradiology* **36**: 382–387

Barkhof F, Filippi M, Miller DH *et al* 1997a Comparison of MR imaging criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* **120**: 2059–2069

Barkhof F, Filippi M, Miller DH *et al* 1997b Strategies for optimizing MRI techniques aimed at monitoring disease activity in multiple sclerosis treatment trials. *J Neurol* **244**: 76–84

Barkhof F, Bruck W, De Groot CJ *et al* 2003a Remyelinated lesions in multiple sclerosis: magnetic resonance image appearance. *Arch Neurol* **60**: 1073–1081

Barkhof F, Rocca M, Francis G *et al* 2003b Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon β1a. *Ann Neurol* **53**: 718–724

Barnard RO, Jellinek EH 1967 Multiple sclerosis with amyotrophy complicated by oligodendroglioma: history of recurrent herpes zoster. *J Neurol Sci* **5**: 441–455

Barned S, Goodman AD, Mattson DH 1995 Frequency of antinuclear antibodies in multiple sclerosis. *Neurology* **45**: 384–385

Barnes D, Hughes R 1997 Oral versus intravenous corticosteroids in acute relapses of multiple sclerosis. Authors response. *Lancet* **349**: 1697

Barnes D, McDonald WI 1992 The ocular manifestations of multiple sclerosis. 2. Abnormalities of eye movements. *J Neurol Neurosurg Psychiatry* **55**: 863–868

Barnes D, McDonald WI, Landon DN, Johnson G 1988 The characterization of experimental gliosis by quantitative nuclear magnetic resonance imaging. *Brain* **111**: 83–94

Barnes D, Munro PM, Youl BD *et al* 1991 The longstanding MS lesion: a quantitative MRI and electron microscopic study. *Brain* **114**: 1271–1280

Barnes D, Hughes RAC, Morris RW *et al* 1997 Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. *Lancet* **349**: 902–906

Barnes MP, Bateman DE, Cleland PG *et al* 1985 Intravenous methylprednisolone for multiple sclerosis in relapse. *J Neurol Neurosurg Psychiatry* **48**: 157–159

Barnett MH, Prineas JW 2004 Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. *Ann Neurol* **55**: 458–468

Barnett MH, Williams DB, Day S *et al* 2003 Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35-year study. *J Neurol Sci* **213**: 1–6

Barnett SC, Alexander CL, Iwashita Y *et al* 2000 Identification of a human olfactory ensheathing cell that can effect transplant-mediated remyelination of demyelinated CNS axons. *Brain* **123**: 1581–1588

Baron JL, Madri JA, Ruddle NH *et al* 1993 Surface expression of α4 integrin by CD4 T cells is required for their entry into brain parenchyma. *J Exp Med* **177**: 57–68

Baron W, Shattil SJ, ffrench-Constant C 2002 The oligodendrocyte precursor mitogen PDGF stimulates proliferation by activation of alpha(v)beta3 integrens. *EMBO J* **21**: 1957–1966

Baron W, Decker L, Colognato H, ffrench-Constant C 2003 Regulation of integrin growth factor interactions in oligodendrocytes by lipid raft microdomains. *Curr Biol* **13**: 151–155

Baron W, Colognato H, ffrench-Constant C 2005 Integrin-growth factor interactions as regulators of oligodendroglial development and function. *Glia* **49**: 467–479

Baron-Van Evercooren A, Avellana-Adalid V, Lachapelle F, Liblau R 1997 Schwann cell transplantation and myelin repair of the CNS. *Mult Scler* **3**: 157–161

Barr D, Kupersmith MJ, Turbin R *et al* 2000 Isolated sixth nerve palsy: an uncommon presenting sign of multiple sclerosis. *J Neurol* **247**: 701–704

Barratt BJ, Payne F, Rance HE *et al* 2002 Identification of the sources of error in allele frequency estimations from pooled DNA indicates an optimal experimental design. *Ann Hum Genet* **66**: 393–405

Barratt HJ, Miller D, Rudge P 1988 The site of the lesion causing deafness in multiple sclerosis. *Scand Audiol* **17**: 67–71

Barres BA, Raff MC 1993 Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. *Nature* **361**: 258–260

Barres BA, Hart IK, Coles HSR *et al* 1992 Cell death and control of cell survival in the oligodendrocyte lineage. *Cell* **70**: 31–46

Barth KA, Kishimoto Y, Rohr KB *et al* 1999 Bmp activity establishes a gradient of positional information throughout the entire neural plate. *Development* **126**: 4977–4987

Bartholdi D, Zumsteg D, Verrips A *et al* 2004 Spinal phenotype of cerebrotendinous xanthomatosis: a pitfall in the diagnosis of multiple sclerosis. *J Neurol* **251**: 105–107

Bartlett PF, Noble MD, Pruss RM *et al* 1981 Rat neural antigen-2 (RAN-2): a cell surface antigen on astrocytes, ependymal cells, Müller cells and lepto-meninges defined by a monoclonal antibody. *Brain Res* **204**: 339–351

Barton A, Woolmore JA, Ward D *et al* 2004 Association of protein kinase C alpha (PRKCA) gene with multiple sclerosis in a UK population. *Brain* **127**: 1717–1722

Barton JJS, Cox TA 1993 Acquired pendular nystagmus in multiple sclerosis: clinical observations and the role of optic neuropathy. *J Neurol Neurosurg Psychiatry* **56**: 262–267

Bartosik-Psujek H, Archelos JJ 2004 Tau protein and 14–3–3 are elevated in the cerebrospinal fluid of patients with multiple sclerosis and correlate with intrathecal synthesis of IgG. *J Neurol* **251**: 414–420

Bartsch U, Peshava P, Raff M, Schachner M 1993 Expression of janusin (J1–160/180) in the retina and optic nerve of the developing and adult mouse. *Glia* **9**: 57–69

Bashir R, Okano M, Kleveland *et al* 1991 SCID/human mouse model of central nervous system lymphoproliferative disease. *Lab Invest* **65**: 702–709

Baskett PJF, Armstrong R 1970 Anaesthetic problems in multiple sclerosis. *Anaesthesia* **25**: 397–401

Bass B, Weinshenker B, Rice GPA *et al* 1988 Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. *Can J Neurol Sci* **15**: 15–19

Basso O, Campi R, Frydenberg M *et al* 2004 Multiple sclerosis in women having children with multiple partners: a population based study in Denmark. *Mult Scler* **10**: 621–625

Bassoe P, Grinker RR 1930 Human rabies and rabies vaccine encephalomyelitis. *Arch Neurol Psychiatry* **23**: 1138–1160

Bastian HC 1882 Special diseases of the spinal cord. In: R Quain (ed.) *A Dictionary of Medicine: Including General Pathology, General Therpaeutics, Hygiene, and the Diseases Peculiar to Women and Children*, by various writers. London: Longmans Green & Co, pp 1479–1483

Bastian HC 1910 Thrombotic softening of the spinal cord: a case of so-called acuter myelitis. *Lancet* **ii**: 1531–1534

Bateman DE, White JE, Elrington G *et al* 1987 Three further cases of Lyme disease. *Br Med J* **294**: 548–549

Bates D, Fawcett PRW, Shaw DA, Weightman D 1978 Polyunsaturated fatty acids in treatment of acute remitting multiple sclerosis. *Br Med J* **2**: 1390–1391

Battistini L, Selmaj K, Kowal C *et al* 1995 Multiple sclerosis: limited diversity of the Vδ2-Jδ3 T-cell receptor in chronic active lesions. *Ann Neurol* **37**: 198–203

Baud O, Greene AE, Li J *et al* 2004 Gutathione peroxidase-catalase cooperativity is required for resistance to hydrogen peroxide by mature rat oligodendocytes. *J Neurosci* **24**: 1531–1540

Bauer H 1953 Über die Bedutung der Papier-Elektrophorese des Liquors fur die clinïsche Forschung. *Dtsch Z Nervenheilk* **170**: 381–401

Bauer HJ 1987 Multiple sclerosis in Europe. Symposium report. *J Neurol* **234**: 195–206

Bauer HJ, Hanefeld FA 1993 *Multiple Sclerosis, Its Impact from Childhood to Old Age*. London: Saunders

Bauer HJ, Firnhaber W, Winkler W 1965 Prognostic criteria in multiple sclerosis. *Ann NY Acad Sci* **122**: 542–551

Bauer HJ, Poser S, Ritter G (eds) 1980 *Progress in Multiple Sclerosis Research*. Berlin: Springer-Verlag, p. 677

Bauer J, Wekerle H, Lassmann H 1995 Apoptosis in brain-specific autoimmune disease. *Curr Opin Immunol* **7**: 839–843

Bauer J, Bradl M, Hickey WF *et al* 1998 T cell apoptosis in inflammatory brain lesions: destruction of T-cells does not depend on antigen recognition. *Am J Pathol* **153**: 715–724

Bauer J, Stadelmann C, Bancher C *et al* 1999 Apoptosis of T-lymphocytes in acute disseminated encephalomyelitis. *Acta Neuropathol* **97**: 543–546

Baumann N, Turpin J-C 2000 Adult-onset leukodystrophies. *J Neurol* **247**: 751–759

Baumhackl U 1995 Multiple sclerosis in lower Austria, prevalence in the city and district of St Poelten. *J Neuroimmunol* **Suppl I**: S57

Baumhackl U, Eibl G, Ganzinger U *et al* 2002 Prevalence of multiple sclerosis in Austria: results of a nationwide survey. *Neuroepidemiology* **21**: 226–234

Baumhefner RW, Tourtellotte WW, Syndulkok P *et al* 1987 Effects of intravenous natural beta interferon on clinical neurofunction, magnetic resonance imaging plaque burden, intrablood-brain barrier IgG synthesis, blood and cerebrospinal fluid cellular immunology and visual evoked responses. *Ann Neurol* **22**: 171

Beall SS, Concannon P, Charmley P *et al* 1989 The germline repertoire of T cell receptor beta chain genes in patients with chronic progressive multiple sclerosis. *J Neuroimmunol* **21**: 59–66

Beall SS, Biddison WE, McFarlin DE *et al* 1993 Susceptibility for multiple sclerosis is determined, in part, by inheritance of a 175-kb region of the TCR Vbeta locus and HLA class II genes. *J Neuroimmunol* **45**: 53–60

Beardsley TL, Brown SVL, Sydnor CF, Grimson BS, Klintworth GK 1984 Eleven cases of sarcoidosis of the optic nerve. *Am J Ophthalmol* **97**: 62–77

Beatty WW, Monson N 1996 Problem solving by patients with multiple sclerosis: comparison of performance on the Wisconsin and California Card Sorting Tests. *J Int Neuropsychol Soc* **2**:134–140.

Beatty WW, Goodkin DE, Monson N *et al* 1988 Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis. *Arch Neurol* **45**: 611–619

Beatty WW, Goodkin DE, Beatty PA, Monson N 1989 Frontal lobe dysfunction and memory impairment in patients with chronic progressive multiple sclerosis. *Brain Cogn* **11**: 73–86

Beaudouin E, Kanny G, Gueant JL *et al* 1992 Anaphylaxie à la carboxymethylcellulose: à propos de deux cas de chocs a des corticoides injectables. *Allerg Immunol* **24**: 333–335

Beaudoin L, Laloux V, Novak J *et al* 2002 NKT cells inhibit the onset of diabetes by impairing the development of pathogenic T cells specific for pancreatic cells. *Immunity* **17**: 725–736

Becchetti A, Gamel K, Torre V 1999 Cyclic nucleotide-gated channels: pore topology studied through the accessibility of reporter cysteines. *J Gen Physiol* **114**: 377–392

Bech E, Lycke J, Gadeberg P *et al* 2002 A randomized, double-blind, placebo-controlled MRI study of anti-herpes virus therapy in MS. *Neurology* **58**: 31–36

Becher B, Durell BG, Noelle RJ 2002 Experimental autoimmune encephalitis and inflammation in the absence of interleukin-12. *J Clin Invest* **110**: 493–497

Becher B, Durell BG, Noelle RJ 2003 IL-23 produced by CNS-resident cells controls T cell encephalitogenicity during the effector phase of experimental autoimmune encephalomyelitis. *J Clin Invest* **112**: 1186–1191

Bechmann I, Steiner B, Gimsa U *et al* 2002 Astrocyte-induced T cell elimination is CD95 ligand dependent. *J Neuroimmunol* **132**: 60–65

Bechtold DA, Smith KJ 2005 Sodium-mediated axonal degeneration in inflammatory demyelinating disease. *J Neurol Sci* **233**: 27–35

Bechtold DA, Davies M, Kapoor R, Smith KJ 2004a Axonal protection in a model of MS: comparison of efficacy of different anticonvulsants. *J Neurol Neurosurg Psychiatry* **75**: 1214

Bechtold DA, Kapoor R, Smith KJ 2004b Axonal protection using flecainide in experimental autoimmune encephalomyelitis. *Ann Neurol* **55**: 607–616

Bechtold DA, Yue X, Evans RM *et al* 2005 Axonal protection in experimental autoimmune neuritis by the sodium channel blocking agent flecainide 1. *Brain* **128:** 18–28

Beck RW, the Optic Neuritis Study Group 1992 Corticosteroid treatment of optic neuritis: a need to change treatment practices. *Neurology* **42**: 1133–1135

Beck RW 1995 The Optic Neuritis Treatment Trial: three-year follow-up results. *Arch Ophthalmol* **113**: 136–137

Beck RW, Cleary PA, Anderson MM *et al* 1992 A randomized controlled trial of corticosteroids in the treatment of acute optic neuritis. *N Engl J Med* **326**: 581–588

Beck RW, Cleary PA, the Optic Neuritis Study Group 1993a Optic neuritis treatment trial. *Arch Ophthalmol* **111**: 773–775

Beck RW, Cleary PA, Trobe JD *et al* 1993b The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J Med* **329**: 1764–1769

Beck RW, Chandler DL, Cole SR *et al* 2002 Interferon beta-1a for early multiple sclerosis: CHAMPS trial subgroup analyses. *Ann Neurol* **51**: 481–490

Beck RW, Trobe JD, Moke PS *et al* 2003 High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch Opthalmol* **121**: 944–949

Beck S, Trowsdale J 2000 The human major histocompatability complex: lessons from the DNA sequence. *Annu Rev Genomics Hum Genet* **1**: 117–137

Becker KG, Simon RM, Bailey-Wilson JE 1998 Clustering of non-major histocompatibility complex susceptibility candidate loci in human autoimmune disease. *Proc Natl Acad Sci USA 95*: 9979–9984

Beebe GW, Kurtzke JF, Kurland LT *et al* 1967 Studies in the natural history of multiple sclerosis. III Epidemiological analysis of the army experience in World War II. *Neurology* **17**: 1–17

Beenakker EA, Oparina TI, Hartgring A *et al* 2001 Cooling garment treatment in MS: clinical improvement and decrease in leukocyte NO production. *Neurology* **57**: 892–894

Beer M, Sandstede J, Weilbach F *et al* 2001 Cardiac metabolism and function in patients with multiple sclerosis: a combined 31P-MR-spectroscopy and MRI study. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* **173**: 399–404

Beer S, Kesselring J 1994 High prevalence of multiple sclerosis in Switzerland. *Neuroepidemiology* **13**: 14–18

Beer S, Rösler KM, Hess CW 1995 Diagnostic value of paraclinical tests in multiple sclerosis: relative sensitivities and specificities for reclassification according to the Poser criteria. *J Neurol Neurosurg Psychiatry* **59**: 152–159

Begovich AB, Helmuth RC, Oksenberg JR *et al* 1990 HLA-DP beta and susceptibility to multiple sclerosis: an analysis of Caucasoid and Japanese patient populations. *Hum Immunol* **28**: 365–372

Behan PO 1977 Diffuse myelitis associated with rubella vaccination. *Br Med J* **1**: 166

Behan PO, Chaudhuri A, Roep BO 2003 The pathogenesis of multiple sclerosis revisited. *J Roy Coll Phys (Edin)* **32**: 244–265

Bejar JM, Ziegler DK 1984 Onset of multiple sclerosis in a 24-month-old child. *Arch Neurol* **41**: 881–882

Belachew S, Aguirre AA, Wang H *et al* 2002 Cyclin-dependent kinase-2 controls oligodendrocyte progenitor cell cycle progression and is downregulated in adult oligodendrocyte progenitors. *J Neurosci* **22**: 8553–8562

Bell MD, Taub DD, Perry VH 1996 Overriding the brain's intrinsic resistance to leucocyte recruitment with intraparenchymal injections of recombinant chemokines. *Neuroscience* **74**: 283–292

Bell RB, Ramachandran S 1995 The relationship of TAP1 and TAP2 dimorphisms to multiple sclerosis susceptibility. *J Neuroimmunol* **59**: 210–214

Bellomi F, Scagnolari C, Tomassini V *et al* 2003 Fate of neutralizing and binding antibodies to IFN beta in MS patients treated with IFN beta for 6 years. *J Neurol Sci* **215**: 3–8

Belopitova L, Guergueltcheva PV, Bojinova V 2001 Definite and suspected multiple sclerosis in children: long-term follow-up and magnetic resonance imaging findings. *J Child Neurol* **16**: 317–324

Ben Hamida M 1977 La sclérose en plaques en Tunisie: étude clinique de 100 observations. *Rev Neurol (Paris)* **33**: 109–117

Bencsik K, Rajda C, Klivenyi P *et al* 1998 The prevalence of multiple sclerosis in the Hungarian city of Szeged. *Acta Neurol Scand* **97**: 315–319

Bencsik K, Rajda C, Fuvesi J *et al* 2001 The prevalence of multiple sclerosis, distribution of clinical forms of the disease and functional status of patients in Csongrad County, Hungary. *Eur Neurol* **46**: 206–209

Ben-Dov N, Hallevy C, Almog Y 2002 Cervical cord syndrome complicating pneumococcal pneumonia. *J Neurol* **249**: 1309–1310

Benedikz JG, Magnusson H, Poser CM *et al* 1991 Multiple sclerosis in Iceland 1900–1985. *J Trop Geogr Neurol* **1**: 16–22

Benedikz JG, Magnusson H, Gudmundsson G 1994 Multiple sclerosis in Iceland, with observations on the alleged epidemic in the Faroe Islands. *Ann Neurol* **36 (Suppl 2)**: S175–S179

Benedikz JG, Stefansson M, Gudmundsson J *et al* 2002 The natural history of untreated multiple sclerosis in Iceland. A total population-based 50 year prospective study. *Clin Neurol Neurosurg* **104**: 208–210

Ben-Hur T, Einstein O, Mizrachi-Kol R *et al* 2003 Transplanted multipotential neural precursor cells migrate into the inflamed white matter in response to experimental autoimmune encephalomyelitis. *Glia* **41**: 73–80

Benito-Leon J, Martin E, Vela L *et al* 1998 Multiple sclerosis in Mostoles, central Spain. *Acta Neurol Scand* **98**: 238–242

Benito-Leon J, Morales JM, Rivera-Navarro J 2002 Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. *Eur J Neurol* **9**: 497–502

Benjelloun N, Charriaut-Marlangue C, Hantaz-Ambroise D *et al* 2002 Induction of cell death in rat brain by a gliotoxic factor from cerebrospinal fluid in multiple sclerosis. *Cell Mol Biol* **48**: 205–212

Benn T, Halfpenny C, Scolding N 2001 Glial cells as targets for cytotoxic immune mediators. *Glia* **36**: 200–211

Bennett L, Hamilton R, Neutel CI *et al* 1977 Survey of persons with multiple sclerosis in Ottawa, 1974–1975. *Can J Public Health* **68**: 141–147

Bennett V, Lambert S 1999 Physiological roles of axonal ankyrins in survival of premyelinated axons and localization of voltage-gated sodium channels. *J Neurocytol* **28**: 303–318

Bennetto L, Totham A, Healy P *et al* 2004 Plasma exchange in episodes of severe inflammatory demyelination of the central nervous system. A report of six cases. *J Neurol* **251**: 1515–1521

Bennetts BH, Teutsch SM, Heard RN *et al* 1995 TAP2 polymorphisms in Australian multiple sclerosis patients. *J Neuroimmunol* **59**: 111–121

Bennetts BH, Teutsch SM, Buhler MM *et al* 1997 The CCR5 deletion mutation fails to protect against multiple sclerosis. *Hum Immunol* **58**: 52–59

Bennetts BH, Teutsch SM, Buhler MM *et al* 1999 HLA-DMB gene and HLA-DRA promoter region polymorphisms in Australian multiple sclerosis patients. *Hum Immunol* **60**: 886–893

Ben-Nun A, Cohen IR 1982 Experimental autoimmune encephalomyelitis (EAE) mediated by T cell lines: process of selection of lines and characterization of the cells. *J Immunol* **129**: 303–308

Ben-Nun A, Wekerle H, Cohen IR 1981a The rapid isolation of clonable antigen-specific T lymphocyte lines capable of mediating autoimmune encephalomyelitis. *Eur J Immunol* **11**: 195–199

Ben-Nun A, Wekerle H, Cohen IR 1981b Vaccination against autoimmune encephalomyelitis using attenuated cells of a T lymphocyte line reactive against myelin basic protein. *Nature* **292**: 60–61

Ben-Nun A, Liblau RS, Cohen L *et al* 1991 Restricted T-cell receptor Vβ gene by myelin basic protein-specific T-cell clones in multiple sclerosis: predominant genes vary in individuals. *Proc Natl Acad Sci USA* **88**: 2466–2470

Ben-Nun A, Mendel I, Bakimer R *et al* 1996 The autoimmune reactivity to myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis is potentially pathogenic: effect of copolymer 1 on MOG-induced disease. *J Neurol* **243**: S14–S22

Benoit P, Douron E, Destel A, Warot P 1986 Spirochaetes and Lyme disease. *Lancet* **ii**: 1223

Benson JM, Campbell KA, Guan Z *et al* 2000 T-cell activation and receptor down-modulation precede deletion induced by mucosally administered antigen. *J Clin Invest* **106**: 1031–1038

van den Berg JS, van Eikema Hommes OR, Wuis EW *et al* 1997 Anaphylactoid reaction to intravenous methylprednisolone in a patient with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **63**: 813–814

Berg D, Maurer M, Warmuth-Metz M *et al* 2000 The correlation between ventricular diameter measured by transcranial sonography and clinical disability and cognitive dysfunction in patients with multiple sclerosis. *Arch Neurol* **57**: 1289–1292

Berg O, Hanley J 1963 Narcolepsy in two cases of multiple sclerosis. *Acta Neurol Scand* **39**: 252–257

Bergamaschi R, Romani A, Tonietti S *et al* 2000 Usefulness of Bayesian graphical models for early prediction of disease progression in multiple sclerosis. *Neurol Sci* **21(Suppl)**: 819–823

Bergamaschi R, Berzuini C, Romani A *et al* 2001 Predicting secondary progression in relapsing–remitting multiple sclerosis: a Bayesian analysis. *J Neurol Sci* **189**: 13–21

Berger BC, Leopold IH 1968 The incidence of uveitis in multiple sclerosis. *Am J Ophthalmol* **62**: 540

Berger JR, Sheremata WA 1983 Persistent neurological deficit precipitated by hot bath test in multiple sclerosis. *J Am Med Assoc* **249**: 1751–1753

Berger JR, Sheremata WA 1985 Reply to letter by F.A Davis. *J Am Med Assoc* **253**: 203

Berger JR, Koralnik IJ 2005 Progressive multifocal leukoencephalopathy and natalizumab – unforeseen consequences. *N Engl J Med* **353**: 414–416

Berger JR, Sheremata WA, Resnick L *et al* 1989 Multiple sclerosis-like illness occurring with human immunodeficiency virus infection. *Neurology* **39**: 324–328

Berger T, Weerth S, Kojima K *et al* 1997 Experimental autoimmune encephalomyelitis: the antigen specificity of T-lymphocytes determines the topography of lesions in the central and peripheral nervous system. *Lab Invest* **76**: 355–364

Berger T, Rubner P, Schautzer F *et al* 2003 Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after the first demyelinating event. *New Engl J Med* **349**: 139–145

Bergerin H, Bakouche P, Chaquat D, Nicolle MH, Reignier A, Nick J 1980 L'atteinte du système nerveux central au cours de la maladie de Behçet. *Semaine Hôpitaux* **56**: 533–538

Bergh FT, Dayyani F, Ziegler-Heitbrock L 2004 Impact of type-I-interferon on monocyte subsets and their differentiation to dendritic cells. An in vivo and ex vivo study in multiple sclerosis patients treated with interferon-beta. *J Neuroimmunol* **146**: 176–188

Bergin JD 1957 Rapidly progressive dementia in disseminated sclerosis. *J Neurol Neurosurg Psychiatry* **20**: 285–292

Bergkvist M, Sandberg-Wolheim M 2001 Serological differences in monozygotic twin pairs discordant for multiple sclerosis. *Acta Neurol Scand* **104**: 262–265

Bergkvist M, Martinsson T, Aman P, Sandberg-Wollheim M 1996 No genetic linkage between multiple sclerosis and the interferon α/β locus. *J Neuroimmunol* **65**: 163–165

Bergkvist M, Olsson M, Sandberg-Wollheim M 2004 No evidence for genetic linkage between development of multiple sclerosis and components of the IFN system and the JAK-STAT pathway. *Mult Scler* **10**: 87–88

Berk C, Constantoyannis C, Honey CR 2003 The treatment of trigeminal neuralgia in patients with multiple sclerosis using percutaneous radiofrequency rhizotomy. *Can J Neurol Sci* **30**: 220–223

Berkman N, Benzarti T, Dhaoui R *et al* 1996 Neuropapillite bilatérale avec décollement séreux du neuroépithélium, au décours d'une vaccination contre l'hépatite B. *Bull Soc Ophtalmol Fr* **96**: 187–189

Berkowitz BW 1985 Matutinal vertigo: clinical characteristics and possible management. *Arch Neurol* **41**: 874–877

Berman M, Feldmann S, Alter M, Zilber N, Kahana E 1981 Acute transverse myelitis:

incidence and aetiologic considerations. *Neurology* **31**: 966–971
Bernardi S, Grasso MG, Bertollini R *et al* 1991 The influence of pregnancy on relapses in multiple sclerosis: a cohort study. *Acta Neurol Scand* **84**: 403–406
Bernheimer H, Budka H, Müller P 1983 Brain tissue immunoglobulins in adrenoleukodystrophy: a comparison with multiple sclerosis and systemic lupus erythematosus. *Acta Neuropathol* **59**: 95–102
Berr C, Dogoujon JM, Clanet M *et al* 1989 A possible new genetic marker associated with a severe course of multiple sclerosis located on chromosome 2: Km. *N Engl J Med* **320**: 467
Berry GT, Kaplan PB, Lichtenstein GR 2000 Hyperammonia possibly due to corticosteroids. *Arch Neurol* **57**: 1085
Bertolene K, Coyle PK, Krupp LB, Doscher CA 1993 Cytokine correlates of fatigue in MS. *Neurology* **43**: A356
Bertolotto A, Malucchi S, Sala A *et al* 2002 Differential effects of three interferon betas on neutralising antibodies in patients with multiple sclerosis: a follow up study in an independent laboratory. *J Neurol Neurosurg Psychiatry* **73**: 148–153
Bertolotto A, Deisenhammer F, Gallo P, Sorensen P 2004 Immunogenicity of interferon beta: differences among products. *J Neurol* **251**: II15–II24
Bertrams J, Kuwert E, Liedtke U 1972 HL-A antigens and multiple sclerosis. *Tissue Antigens* **2**: 405–408
Besser M, Wank R 1999 Clonally restricted production of the neurotrophins brain-derived neurotrophic factor and neurotrophin-3 mRNA by human immune cells and Th1/Th2-polarized expression of their receptors. *J Immunol* **162**: 6303–6306
Bethoux F, Miller DM, Kinkel RP 2001 Recovery following acute exacerbations of multiple sclerosis: from impairment to quality of life. *Mult Scler* **7**: 137–142
Bettelli E, Prabhu Das MR, Howard ED *et al* 1998 IL-10 is critical in the regulation of autoimmune encephalomyelitis as demonstrated by studies of IL-10- and IL-4-deficient and transgenic mice. *J Immunol* **161**: 3299–3306
Bettelli E, Pagany M, Weiner HL *et al* 2003 Myelin oligodendrocyte glycoprotein-specific T cell receptor transgenic mice develop spontaneous autoimmune optic neuritis. *J Exp Med* **197**: 1073–1081
Betts CD, D'Mellow MT, Fowler CJ 1993 Urinary symptoms and the neurological features of bladder dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **56**: 245–250
Betts CD, Jones SJ, Fowler CG, Fowler CJ 1994 Erectile dysfunction in multiple sclerosis: associated neurological and neurophysical deficits, and treatment of the condition. *Brain* **117**: 1303–1310
Beutler E, Sipe JC, Romine JS *et al* 1996 The treatment of chronic progressive multiple sclerosis with cladribine. *Proc Natl Acad Sci USA* **93**: 1716–1720
Bevan Lewis W 1897 The structure of the first or outermost layer of the cerebral cortex. *Edinb Med J* **1**: 573–592
Bever CT 1994 The current status of studies of aminopyridines in patients with multiple sclerosis. *Ann Neurol* **36**: S118–S121
Bever CT, Leslie J, Camenga D, Panitch HS, Johnson KP 1990 Preliminary trial of 3,4-aminopyridine in patients with multiple sclerosis. *Ann Neurol* **27**: 421–427
Bever CT, Young D, Anderson PA *et al* 1994 The effects of 4-aminopyridine in multiple sclerosis patients: results of a randomised, placebo-controlled, double-blind, concentration-controlled, crossover trial. *Neurology* **44**: 1504–1509
Bezman L, Moser AB, Raymond GV *et al* 2001 Adrenoleucodystrophy: incidence, new mutation rate and results of extended family screening. *Ann Neurol* **49**: 512–517
Bhakoo KK, Pearce D 2000 In vitro expression of N-acetyl aspartate by oligodendrocytes: implications for proton magnetic resonance spectroscopy signal in vivo. *J Neurochem* **74**: 254–262
Bharucha NE, Bharucha EP, Wadia HN *et al* 1988 Prevalence of multiple sclerosis in the Parsis of Bombay. *Neurology* **38**: 727–729
Bhatia KP, Brown P, Gregory R *et al* 1995 Progressive myoclonic ataxia associated with coeliac disease. The myoclonus is of cortical origin but the pathology is in the cerebellum. *Brain* **118**: 1087–1093
Bhatti MT, Newman NJ 1999 A multiple sclerosis-like illness in a man harboring the mtDNA 14484 mutation. *J Neuroophthalmol* **19**: 28–33
Bhigjee AI 1987 Multiple sclerosis in a black patient: a case report. *S Afr Med J* **72**: 873–875
Bianchi M, Sacerdote P, Ricciardi-Castagnoli P *et al* 1992 Central effects of tumor necrosis factor alpha and interleukin-1 alpha on nociceptive thresholds and spontaneous locomotor activity. *Neurosci Lett* **148**: 76–80
Bickerstaff ER, Small JM, Guest IA 1958 The relapsing course of certain meningiomas in relation to pregnancy and menstruation. *J Neurol Neurosurg Psychiatry* **21**: 89–91
Biddison WE, Taub DD, Cruikshank WW, Center SM, Connor EW, Honma K 1997 Chemokine and matrix metalloproteinase secretion by myelin proteolipid protein-specific $CD8^+$ T cells: potential roles in inflammation. *J Immunol* 158: 3046–3053
Bieber AJ, Warrington A, Pease LR, Rodriguez M 2001 Humoral autoimmunity as a mediator of CNS repair. *Trends Neurosci* **24**: S39–S44
Bieber AJ, Warrington A, Asakura K *et al* 2002 Human antibodies accelerate the rate of remyelination following lysolecithin-induced demyelination in mice. *Glia* **37**: 241–249
Bieber AJ, Kerr S, Rodriguez M 2003 Efficient central nervous system remyelination requires T cells. *Ann Neurol* **53**: 680–684
Bielecki B, Mycko M, Tronczyńska E *et al* 2003 A whole genome screen for association in Polish multiple sclerosis patients. *J Neuroimmunol* **143**: 107–111
Bielefeldt K, Whiteis CA, Chapleau MW, Abboud FM 1999 Nitric oxide enhances slow inactivation of voltage-dependent sodium currents in rat nodose neurons. *Neurosci Lett* **271**: 159–162
Bielekova B, Martin R 2004 Development of biomarkers in multiple sclerosis. *Brain* **27**: 1463–1478
Bielekova B, Goodwin B, Richert N *et al* 2000 Encephalitogenic potential of the myelin basic protein peptide (amino acids 83–99) in multiple sclerosis: results of a phase II clinical trial with an altered peptide ligand. *Nature Med* **6**: 1167–1175
Bielekova B, Richert N, Howard T *et al* 2004 Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon β. *Proc Natl Acad Sci USA* **101**: 8705–8708
Bielschowsky M 1903 Zür Histologie der multiplen Sklerose. *Neurolisches Zentralblatt* **22**: 770–777
Bien CG, Bauer J, Deckwerth TL *et al* 2002 Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. *Ann Neurol* **51**: 311–318
Bienfang DC, Kantrowitz FG, Noble JL, Raynor AM 1977 Ocular abnormalities after influenza immunization. *Arch Ophthalmol* **95**: 1649
Bignami A, Gherardi D, Gallo D 1961 Sclerosi a placche acuta a localizzazone ipotalamica con sintomalogia psichica di tip malincolinco. *Riv Neurol* **31**: 240–268
Bilinska M, Frydecka I, Noga L *et al* 2004 Progression of multiple sclerosis is associated with exon 1 CTLA-4 gene polymorphism. *Acta Neurol Scand* **110**: 67–71
Billiau A, Heremans H, Vanderkerckhove F *et al* 1988 Enhancement of experimental allergic encephalomyelitis in mice by antibodies against IFN-gamma. *J Immunol* 140: 1506–1510
Billiau A, Kieseier BC, Hartung HP 2004 Biologic role of interferon beta in multiple sclerosis. *J Neurol* **251**: II10–II14
Billon N, Terrinoni A, Jolicoeur C *et al* 2004 Roles for p53 and p73 during oligodendrocyte development. *Development* **131**: 1211–1220
Bing R, Reese H 1926 Die MultipleSclerose in der nord west Schwiez. *Schweiz Med Wochenschr* **56**: 30–34
Binzer M, Forsgren L, Holmgren G *et al* 1994 Familial clustering of multiple sclerosis in a northern Swedish rural district. *J Neurol Neurosurg Psychiatry* **57**: 497–499
Biousse V, Trichet C, Bloch-Michel E, Roullet E 1999 Multiple sclerosis associated with uveitis in two large clinic-based series. *Neurology* **52**: 179–181
Birk K, Rudick R 1986 Pregnancy and multiple sclerosis. *Arch Neurol* **43**: 719–726

Birk K, Ford C, Smeltzer S *et al* 1990 The clinical course of multiple sclerosis during pregnancy and the puerperium. *Arch Neurol* **47**: 738–742

Birkhead R, Friedmam JH 1987 Hiccups and vomiting as initial manifestations of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **50**: 232–233

Birnbaum G, van Ness B 1992 Quantitation of T-cell receptor V beta chain expression on lymphocytes from blood, brain, and spinal fluid in patients with multiple sclerosis and other neurological diseases. *Ann Neurol* **32**: 24–30

Bishop A, Anderson JE 2005 NO signaling in the CNS: from the physiological to the pathological. *Toxicology* **208:** 193–205

Bitar D, Whitacre CC 1988 Suppression of experimental autoimmune encephalomyelitis by the oral administration of myelin basic protein. *Cell Immunol* **112**: 364–370

Bitsch A, Wegener C, da Costa C *et al* 1999 Lesion development in Marburg's type of acute multiple sclerosis: from inflammation to demyelination. *Mult Scler* **5**: 138–146

Bitsch A, KuhlmannT, Da Costa C *et al* 2000a Tumour necrosis factor alpha mRNA expression in early multiple sclerosis lesions: correlation with demyelinating activity and oligodendrocyte pathology. *Glia* **29**: 366–375

Bitsch A, Schuchardt J, Bunkowski S *et al* 2000b Acute axonal injury in multiple sclerosis: correlation with demyelination and inflammation. *Brain* **123**: 1174–1183

Bitsch A, Kuhlmann T, Stadelmann C *et al* 2001 A longitudinal MRI study of histopathologically defined hypointense multiple sclerosis lesions. *Ann Neurol* **49**: 793–796

Bitti PP, Murgia BS, Ticca A *et al* 2001 Association between the ancestral haplotype HLA A30B18DR3 and multiple sclerosis. *Genet Epidemiol* **20**: 271–283

Bizzi A, Ulug AM, Crawford TO *et al* 2001 Quantitative proton MR spectroscopic imaging in acute disseminated encephalomyelitis. *Am J Neuroradiol* **22**: 1125–1130

Bizzozero OA, DeJesus G, Bixler HA *et al* 2005 Evidence of nitrosative damage in the brain white matter of patients with multiple sclerosis. *Neurochem Res* **30:** 139–149

Bjartmar C, Kidd G, Mork S *et al* 2000 Neurological disability correlates with spinal cord axonal loss and reduced N-acetyl aspartate in chronic multiple sclerosis patients. *Ann Neurol* **48**: 893–901

Bjartmar C, Kinkel RP, Kidd G *et al* 2001 Axonal loss in normal-appearing white matter in a patient with acute MS. *Neurology* **57**: 1248–1252

Bjartmar C, Wujek JR, Trapp BD 2003 Axonal loss in the pathology of MS: consequences for understanding the progressive phase of the disease. *J Neurol Sci* **206**: 165–171

Bjerrum OW, Bach FW, Zeeberg I 1988 Increased level of cerebrospinal fluid beta 2-microglobulin is related to neurologic impairment in multiple sclerosis. *Acta Neurol Scand* **78**: 72–75

Björkman PJ 1997 MHC restriction in three dimensions: a view of T cell receptor/ligand interactions. *Cell* **89**: 167–170

Björkman PJ, Saper MA, Samraoui B *et al* 1987 Structure of the human class I histocompatibility antigen. *Nature* **329**: 506–512

Björnson CRR, Rietze RL, Reynolds BA *et al* 1999 Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells in vivo. *Science* **283**: 534–537

Black JA, Waxman SG 1996 Sodium channel expression: a dynamic process in neurons and non-neuronal cells. *Dev Neurosci* **18**: 139–152

Black JA, Felts P, Smith KJ *et al* 1991 Distribution of sodium channels in chronically demyelinated spinal cord axons: immuno-ultrastructral localization and electrophysiological observations. *Brain Res* **544**: 59–70

Black JA, Sontheimer H, Waxman SG 1993 Spinal cord astrocytes *in vitro*: phenotypic diversity and sodium channel immunoreactivity. *Glia* **7**: 272–285

Black JA, Cummins TR, Plumpton C *et al* 1999a Upregulation of a silent sodium channel after peripheral, but not central, nerve injury in DRG neurons. *J Neurophysiol* **82**: 2776–2785

Black JA, Fjell J, Dib-Hajj S *et al* 1999b Abnormal expression of SNS/PN3 sodium channel in cerebellar Purkinje cells following loss of myelin in the taiep rat. *NeuroReport* **10**: 913–918

Black JA, Dib-Hajj S, Baker D *et al* 2000 Sensory neuron-specific sodium channel SNS is abnormally expressed in the brains of mice with experimental allergic encephalomyelitis and humans with multiple sclerosis. *Proc Natl Acad Sci USA* **97**: 11598–11602

Blackburn-Munro G, Fleetwood-Walker SM 1999 The sodium channel auxiliary subunits beta1 and beta2 are differentially expressed in the spinal cord of neuropathic rats. *Neuroscience* **90**: 153–164

Blake G, Murphy S 1997 Onset of myasthenia gravis in a patient with multiple sclerosis during interferon-1b treatment. *Neurology* **49**: 1747–1748

Blakemore WF 1976 Invasion of Schwann cells into the spinal cord of the rat following local injections of lysolecithin. *Neuropathol Appl Neurobiol* **2**: 21–39

Blakemore WF 2000 Olfactory glia and CNS repair: a step in the road from proof of principle to clinical application. *Brain* **123**: 1543–1544

Blakemore WF, Franklin RJM 2000 Transplantation options for therapeutic central nervous system remyelination. *Cell Transplantation* **9**: 289–294

Blakemore WF, Smith KJ 1983 Node-like axonal specializations along demyelinated central nerve fibres: ultrastructural observations. *Acta Neuropathol* **60**: 291–296

Blakemore WF, Eames RA, Smith KJ, McDonald WI 1977 Remyelination in the spinal cord of the cat following intraspinal injections of lysolecithin. *J Neurol Sci* **33**: 31–43

Blakemore WF, Gilson JM, Crang AJ 2000 Transplanted glial cells migrate over a greater distance and remyelinate demyelinated lesions more rapidly than endogenous remyelinating cells. *J Neurosci Res* **61**: 288–294

Blakemore WF, Chari DM, Gilson JM, Crang AJ 2002 Modelling large areas of demyelination in the rat reveals the potential and possible limitations of transplanted glial cells for remyelination in the CNS. *Glia* **38**: 155–168

Blakemore WF, Gilson JM, Crang AJ 2003 The presence of astrocytes in areas of demyelination influences remyelination following transplantation of oligodendrocyte progenitors. *Exp Neurol* **184**: 955–963

Blanc M, Clanet M, Berr C *et al* 1986 Immunoglobulin allotypes and susceptibility to multiple sclerosis. *J Neurol Sci* **75**: 1–5

Blanco Y, Yague J, Graus F, Saiz A 2003 No association of inducible nitric oxide synthase gene (NOS2A) to multiple sclerosis. *J Neurol* **250**: 598–600

Blanco Y, Saiz A, Carreras E, Graus F 2005 Autologous haematopoietic-stem-cell transplantation for multiple sclerosis. *Lancet Neurol* **4**: 54–63

Blankenhorn EP, Butterfield RJ, Rigby R *et al* 2000 Genetic analysis of the influence of pertussis toxin on experimental allergic encephalomyelitis susceptibility: an environmental agent can override genetic checkpoints. *J Immunol* **164**: 3420–3425

Blasko I, Stampfer-Kountchev M, Robatscher P *et al* 2004 How chronic inflammation can affect the brain and support the development of Alzheimer's disease in old age: the role of microglia and astrocytes. *Aging Cell* **3**: 169–176

Blenow K, Fredman P, Wallin A *et al* 1994 Formulas for the quantitation of intrathecal IgG production: their validity in the presence of blood-brain barrier damage and their utility in multiple sclerosis. *J Neurol Sci* **121**: 90–96

Blight AR, Toombs JP, Bauer MS, Widmer WR 1991 The effects of 4-aminopyridine on neurological deficits in chronic cases of traumatic spinal cord injury in dogs: a phase I clinical trial. *J Neurotrauma* **8**: 103–119

Blinkenberg M, Rune K, Jemsen CV *et al* 2000 Cortical cerebral metabolism correlates with MRI lesion load and cognitive dysfunction in MS. *Neurology* **54**: 558–564

Blocq P, Londe A 1890 Anatomie pathologique de la moelle épinière. *Nouv Iconographie Salpétrière* **3**: 309–312

Bloor JW, Johnson RJ, Canales L, Dunn DP 1974 Reversible paralysis of automatic respiration. *Arch Neurol* **34**: 686–689

Bluestone JA, Khattri R, Sciammas R, Sperling AI 1995 TCRγδ cells: a specialized T-cell subset in the immune system. *Annu Rev Cell Biol* **11**: 307–353

Blumberg BM, Mock DJ, Powers JM *et al* 2000 The HHV6 paradox: ubiquitous commensal or insidious pathogen? A two step in situ PCR approach. *J Clin Virol* **16**: 159–178

Blumen SC, Bevan S, Abu-Mouch S *et al* 2003 A locus for complicated hereditary spastic paraplegia maps to chromosome 1q24–1q32. *Ann Neurol* **54**: 796–203

Blumhardt LD, Barrett G, Halliday AM 1982 The pattern visual evoked potential in the clinical assessment of undiagnosed spinal cord disease. *Adv Neurol* **37**: 463–471

Bo L, Mork S, Kong PA *et al* 1994 Detection of MHC class II-antigens on macrophages and microglia, but not on astrocytes and endothelia in active multiple sclerosis lesions. *J Neuroimmunol* **51**: 135–146

Bo L, Vedeler CA, Nyland HI *et al* 2003a Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *J Neuropathol Exp Neurol* **62**: 723–732

Bo L, Vedeler CA, Nyland H *et al* 2003b Intracortical multiple sclerosis lesions are not associated with increased lymphocyte infiltration. *Mult Scler* **9**: 323–331

Bobowick AR, Kurtzke JF, Brody JA *et al* 1978 Twin study of multiple sclerosis: an epidemiologic inquiry. *Neurology* **28**: 978–987

Bocko D, Bilinska M, Dobosz T *et al* 2003 Lack of association between an exon 1 CTLA-4 gene polymorphism A(49)G and multiple sclerosis in a Polish population of the Lower Silesia region. *Arch Immunol Ther Exp* **51**: 201–205

Bode MK, Tikkakoski T, Tuisku S *et al* 2001 Isolated neurosarcoidosis – MR findings and pathological correlation. *Acta Radiol* **42**: 563–567

Boden G 1948 Radiation myelitis of the cervical spinal cord. *Br J Radiol* **21**: 464–469

Boehm T, Scheu S, Pfeffer K, Bleul CC 2003 Thymic medullary epithelial cell differentiation, thymocyte emigration, and the control of autoimmunity require lympho-epithelial cross talk via LTbR. *J Exp Med* **198**: 757–769

von Boehmer H 1992 Thymic selection: a matter of life and death. *Immunol Today* **13**: 454–458

von Boehmer H, Teh HS, Kisielow P 1989 The thymus selects the useful, neglects the useless and destroys the harmful. *Immunol Today* **10**: 57–61

Boggild MD, Williams R, Haq N, Hawkins CP 1996 Cortical plaques visualised by fluid-attenuated inversion recovery imaging in relapsing multiple sclerosis. *Neuroradiology* **38**: S10–S13

Boghen D, Sebag M, Michaud J 1988 Paraneoplastic optic neuritis and encephalomyelitis: report of a case. *Arch Neurol* **45**: 353–356

Bogousslavsky J, Hungerbüler JP, Regli F, Graf HJ 1982 Subacute myelopathy as the presenting manifestation of sarcoidosis. *Acta Neurochir* **65**: 193–197

Bogue M, Candéias S, Benoist C, Mathis D 1991 A special repertoire of a:b T cells in neonatal mice. *EMBO J* **10**: 3647–3654

Boiko AN 1994 Multiple sclerosis prevalence in Russia and other countries of the former USSR. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 219–230

Boiko AN, Deomina T, Favorava O *et al* 1995 Epidemiology of multiple sclerosis in Russia and other countries of the former Soviet Union: investigations of environmental and genetic factors. *Acta Neurol Scand* **161 (Suppl)**: 71–76

Boiko AN, Gusev EI, Sudomoina MA *et al* 2002 Association and linkage of juvenile MS with HLA-DR2(15) in Russians. *Neurology* **58**: 658–660

Boiko T, Rasband MN, Levinson SR *et al* 2001 Compact myelin dictates the differential targeting of two sodium channel isoforms in the same axon. *Neuron* **30**: 91–104

Bolanos JP, Peuchen S, Heales SJ *et al* 1994 Nitric oxide-mediated inhibition of the mitochondrial respiratory chain in cultured astrocytes. *J Neurochem* **63**: 910–916

Bolanos JP, Almeida A, Stewart V *et al* 1997 Nitric oxide-mediated mitochondrial damage in the brain: mechanisms and implications for neurodegenerative diseases. *J Neurochem* **68**: 2227–2240

Bolger C, Bojanic S, Sheahan N *et al* 2000 Ocular microtremor (OMT): a new neurophysiological approach to multiple sclerosis. *J Neurol Neurosurg Psychiatry* **68**: 639–642

Bolotina VM, Najibi S, Palacino JJ *et al* 1994 Nitric oxide directly activates calcium-dependent potassium channels in vascular smooth muscle. *Nature* **368**: 850–853

Bolviken B, Celius EG, Nilsen R, Strand T 2003 Radon: a possible risk factor in multiple sclerosis. *Neuroepidemiology* **22**: 87–94

Boman J, Roblin PM, Sundstrom P *et al* 2000 Failure to detect *Chlamydia pneumoniae* in the central nervous system of patients with MS. *Neurology* **54**: 265

Bombardier CH, Blake KD, Ehde DM *et al* 2004 Alcohol and drug abuse among persons with multiple sclerosis. *Mult Scler* **10**: 35–40

Bon CL, Garthwaite J 2003 On the role of nitric oxide in hippocampal long-term potentiation. *J Neurosci* **23**: 1941–1948

Bonduelle M 1967 Les formes bénignes de la sclérose en plaques. *Presse Med* **75**: 2023–2026

Bonduelle M, Albaranès R 1962 Etude statistique de 145 cas de la sclérose en plaques. *Semaine Hôpitaux* **38**: 3762–3773

Bonduelle M, Bouygues P, Sallou C 1954 La sclérose en plaques chez l'enfant. *Presse Med* **62**: 563–564

Bonduelle M, Bouygues P, Chaumont P 1964 Amyotrophies et abolition des réflexes dans la sclérose en plaques. *Sémaine Hôpitaux* **40**: 814–821

Bonetti B, Raine CS 1997 Multiple sclerosis: oligodendrocytes display cell death-related molecules *in situ* but do not undergo apoptosis. *Ann Neurol* **42**: 74–84

Bonetti B, Stegagno C, Cannella B *et al* 1999 Activation of NF-kappaB and c-jun transcription factors in multiple sclerosis lesions: implications for oligodendrocyte pathology. *Am J Pathol* **155**: 1433–1438

Bonilla S, Alarcon P, Villaverde R *et al* 2002 Haematopoietic progenitor cells from adult bone marrow differentiate into cells that express oligodendroglial antigens in the neonatal mouse brain. *Eur J Neurosci* **15**: 575–582

Boon M, Nolte IM, Bruinenberg M *et al* 2001 Mapping of a susceptibility gene for multiple sclerosis to the 51 kb interval between G511525 and D6S1666 using a new method of haplotype sharing analysis. *Neurogenetics* **3**: 221–230

Booss J, Esiri MM, Tourtellotte WW, Mason DY 1983 Immunohistological analysis of T lymphocyte subsets in the central nervous system in chronic progressive multiple sclerosis. *J Neurol Sci* **62**: 219–232

Borello-France D, Leng W, O'Leary M *et al* 2004 Bladder and sexual function among women with multiple sclerosis. *Mult Scler* **10**: 455–461

Borg-Stein J, Pine ZM, Miller JR, Brin MF 1993 Botulinum toxin for the treatment of spasticity in multiple sclerosis. *Am J Phys Med Rehab* **72**: 364–368

Bornstein MB, Appel SH 1961 The application of tissue culture to the study of experimental 'allergic' encephalomyelitis. I. Patterns of demyelination. *J Neuropathol Exp Neurol* **20**: 141–147

Bornstein MB, Crain SM 1965 Functional studies of cultured brain tissues as related to 'demyelinative disorders'. *Science* **148**: 1242–1244

Bornstein MB, Miller A, Teitelbaum D *et al* 1982 Multiple sclerosis: trial of a synthetic polypeptide. *Ann Neurol* **11**: 317–319

Bornstein MB, Miller A, Slagle S *et al* 1987 A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. *N Engl J Med* **317**: 408–414

Bornstein MB, Miller A, Slagle S *et al* 1991 A placebo-controlled double-blind randomised two-center, pilot trial of Cop-1 in chronic progressive multiple sclerosis. *Neurology* **41**: 533–539

Borodic GE, Ferrante R, Wiegener AW, Young RR 1992 Treatment of spasticity with botulinum toxin. *Ann Neurol* **31**: 113

Borrás C, Rio J, Porcel J *et al* 1999 Emotional state of patients with relapsing–remitting MS treated with interferon beta-1b. *Neurology* **52**: 1636–1639

Borst M 1903 Die multiple Sklerose des Zentralnervensystem. *Ergebn allg Path Menschen Tieres* **9**: 67–187

Boskovich SA, Lowder CY, Meisler DM, Gutman FA 1993 Systemic diseases associated with intermediate uveitis. *Cleveland Clin J Med* **60**: 460–465

Bosma R, Wynia K, Havlikova E *et al* 2005 Efficacy of desmopressin in patients with multiple sclerosis suffering from bladder

dysfunction: a meta-analysis. *Acta Neurol Scand* **112**: 1–5
Bostock H 1984 Internodal conduction along undissected nerve fibers in experimental neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R (eds) *Peripheral Neuropathy*. Philadelphia: W.B Saunders, pp. 900–910
Bostock H 1993 Impulse propagation in experimental neuropathy. In: Dyck PJ, Thomas PK, Griffin JW *et al* (eds) *Peripheral Neuropathy*. Philadelphia: W.B Saunders, pp. 109–120
Bostock H 1994 The pathophysiology of demyelination. In: Herndon RM, Seil FJ (eds) *Multiple Sclerosis: Current Status of Research and Treatment*. New York: Demos Publications, pp. 89–112
Bostock H, Grafe P 1985 Activity-dependent excitability changes in normal and demyelinated rat spinal root axons. *J Physiol* **365**: 239–257
Bostock H, Rothwell JC 1997 Latent addition in motor and sensory fibres of human peripheral nerve. *J Physiol* **498**: 277–294
Bostock H, Sears 1976 Continuous conduction in demyelinated mammalian nerve fibres. *Nature* **263**: 786–787
Bostock H, Sears 1978 The internodal axon membrane: electrical excitability and continuous conduction in segmental demyelination. *J Physiol* **280**: 273–301
Bostock H, Sherratt RM, Sears TA 1978 Overcoming conduction failure in demyelinated nerve fibres by prolonging action potentials. *Nature* **274**: 385–387
Bostock H, Hall SM, Smith KJ 1980 Demyelinated axons can form 'nodes' prior to remyelination. *J Physiol* **308**: 21–23
Bostock H, Sears TA, Sherratt RM 1981 The effects of 4-aminopyridine and tetraethylammonium ions on normal and demyelinated mammalian nerve fibres. *J Physiol* **313**: 301–315
Bostock H, Cikurel K, Burke D 1998 Threshold tracking techniques in the study of human peripheral nerve. *Muscle Nerve* **21**: 137–158
Bot JCJ, Barkhof F, Lycklama G *et al* 2000 Comparison of a conventional cardiac-triggered dual spin-echo and a fast STIR sequence in detection of spinal cord lesions in multiple sclerosis. *Eur Radiol* **10**: 753–758
Bot JCJ, Barkhof F, Lycklama G *et al* 2002 Differentiation of multiple sclerosis from other inflammatory disorders and cerebrovascular disease: value of spinal MR imaging. *Radiology* **223**: 46–56
Bot JCJ, Barkhof F, Polman CH *et al* 2004 Spinal cord abnormalities in newly diagnosed MS patients: added value of spinal MRI examination. *Neurology* **62**: 226–233
Botstein DR, Risch N 2003 Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. *Nature Genet* **33**: 228–237
Botstein DR, White RL, Skolnick MH, Davis R 1980 Construction of a genetic map in humans. *Am J Hum Genet* **32**: 314–331
Boudouresques J, Khalil R, Cherif AA *et al* 1975 Epilepsie et sclérose en plaques. *Rev Neurol* **131**: 729–735
Bourneville DM, Guerard L 1869 *De la sclérose en plaques disseminées*. Paris: Delahaye
Bourneville DM, Regnard PML 1876–1880 *Iconographie photographique de la Salpétrière*. Service de M. Charcot, 3 vols
Bourquin C, Schubart A, Tobollik S *et al* 2003 Selective unresponsiveness to conformational B cell epitopes of the myelin oligodendrocyte glycoprotein in H-2(b) mice. *J Immunol* **171**: 455–461
Bouslama-Oueghlani L, Wehrle R, Sotelo C, Dusart I 2003 The developmental loss of the ability of Purkinje cells to regenerate their axons occurs in the absence of myelin: an in vitro model to prevent myelination. *J Neurosci* **23**: 8318–81329
Bousso P, Bhakta NR, Lewis RS, Robey E 2002 Dynamics of thymocyte-stromal cell interactions visualized by two-photon microscopy. *Science* **296**: 1876–1880
Boutin B, Esquivel E, Mayer M *et al* 1988 Multiple sclerosis in children: report of clinical and paraclinical features of 19 cases. *Neuropediatrics* **19**: 118–123
Bowden AN, Bowden PMA, Friedman AL, Perkin GD, Rose FC 1974 A trial of cortocotrophin gelatin injection in acute optic neuritis. *J Neurol Neurosurg Psychiatry* **37**: 869–873
Bowe CM, Kocsis JD, Targ EF, Waxman SG 1987 Physiological effects of 4-aminopyridine on demyelinated mammalian motor and sensory fibers. *Ann Neurol* **22**: 264–268
Boyd JG, Lee J, Skihar V *et al* 2004 LacZ-expressing olfactory ensheathing cells do not associate with myelinated axons after implantation into the compressed spinal cord. *Proc Natl Acad Sci USA* **101**: 2162–2166
Boylan KK, Takahashi N, Diamond M *et al* 1987 DNA length polymorphism located 5' to the human myelin basic protein gene. *Am J Hum Genet* **40**: 387–400
Boylan KK, Takahashi N, Paty D *et al* 1990 DNA length polymorphism 5' to the myelin basic protein gene is associated with multiple sclerosis. *Ann Neurol* **27**: 291–297
Boyle EA, McGeer PL 1990 Cellular immune response in multiple sclerosis plaques. *Am J Pathol* **137**: 575–584
Boyle ME, Berglund EO, Murai KK *et al* 2001 Contactin orchestrates assembly of the septate-like junctions at the paranode in myelinated peripheral nerve. *Neuron* **30**: 385–397
Boz C, Velioglu S, Ozmenoglu M 2003 Acute disseminated encephalomyelitis after bee sting. *Neurol Sci* **23**: 313–315
Bozek CB, Kastrukoff CF, Wright JM, Perry TL, Larsen TA 1987 A controlled trial of isoniazid therapy for action tremor in multiple sclerosis. *J Neurol* **234**: 36–39
Bozzali M, Cercignani M, Sormani MP *et al* 2002 Quantification of brain grey matter damage in different MS phenotypes by use of diffusion tensor MR imaging. *Am J Neuroradiol* **23**: 985–988
Bradbury EJ, Moon LDF, Popat RJ *et al* 2002 Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* **416**: 636–640
Bradbury M 1979 *The Concept of the Blood Brain Barrier*. New York: John Wiley
Bradbury M, Cserr HF 1985 Drainage of cerebral interstitial fluid of cerebrospinal fluid into lymphatics. In: Johnston MG (ed.) *Experimental Biology of the Lymphatic Circulation*. Amsterdam: Elsevier, pp. 355–394
Bradley WG, Whitty CWM 1967 Acute optic neuritis: its clinical features and their relation to prognosis for recovery of vision. *J Neurol Neurosurg Psychiatry* **30**: 531–538
Bradley WG, Whitty CWM 1968 Acute optic neuritis: prognosis for development of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **31**: 10–18
Brady CM, DasGupta R, Dalton C *et al* 2004 An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler* **10**: 425–433
Brady ST, Witt AS, Kirkpatrick LL *et al* 1999 Formation of compact myelin is required for maturation of the axonal cytoskeleton. *J Neurosci* **19**: 7278–7288
Brahic M, Bureau J-F 1997 Multiple sclerosis and retroviruses. *Ann Neurol* **42**: 984–985
Brain WR 1930 Critical review: disseminateed sclerosis. *Q J Med* 23: 343–391
Brain WR 1933 *Diseases of the Nervous System*, 1st edn. London: Oxford University Press, pp. 350–361, 366–369, 389–402
Brain WR 1936 Prognosis of disseminated sclerosis. *Lancet* **2**: 866–867
Brain WR 1940 *Diseases of the Nervous System*, 2nd edn. London: Oxford University Press, pp. 469–505
Brain WR, Wilkinson M 1957 The association of cervical spondylosis and disseminated sclerosis. *Brain* **80**: 456–478
Bramanti P, Sessa E, Rifici C *et al* 1998 Enhanced spasticity in primary progressive MS patients treated with interferon beta-1b. *Neurology* **51**: 1720–1723
Bramwell B 1903 On the relative frequency of disseminated sclerosis in this country (Scotland and the North of England) and in America. *Rev Neurol Psych Edinb* **i**: 12–17
Bramwell B 1917 The prognosis in disseminated sclerosis; duration in two hundred cases of disseminated sclerosis. *Edinb Med J* **18**: 15–23
Brand A, Richter-Landsberg C, Leibfritz D 1993 Multinuclear NMR studies on the energy metabolism of glial and neuronal cells. *Dev Neurosci* **15**: 289–298
Brandt JT, Triplett DA, Alving B, Scharrer I 1995 Criteria for the diagnosis of lupus anticoagulants: an update. *Thromb Hemost* **74**: 1185–1190

Brandt S, Gyldensted C, Offner H, Melchior JC 1981 Multiple sclerosis with onset in a two-year-old boy. *Neuropediatrics* **12**: 75–82

Brard F, Shannon M, Luning Prak E *et al* 1999 Somatic mutation and light chain rearrangement generate autoimmunity in anti-single-stranded DNA transgenic MRL/*lpr* mice. *J Exp Med* **190**: 691–704

Brass SD, Caramanos Z, Santos C *et al* 2003 Multiple sclerosis vs acute disseminated encephalomyelitis in childhood. *Pediatr Neurol* **29**: 227–231

Brassat D, Azais-Vuillemin C, Yaounag J *et al* 1999 Familial factors influence disability in MS multiplex families. French Multiple Sclerosis Genetics Group. *Neurology* **52**: 1632–1636

Brassat D, Recher C, Waubant E *et al* 2002 Therapy-related acute myeloblastic leukemia after mitoxantrone treatment in a patient with MS. *Neurology* **59**: 954–955

Brassington JC, Marsh NV 1998 Neuropsychological aspects of multiple sclerosis. *Neuropsychol Rev* **8**: 43–77

Bräuer AU, Savaskan NE, Kühn H *et al* 2003 A new phospolipid phosphatase, PRG-1, is involved in axon growth and regenerative sprouting. *Nat Neurosci* **6**: 572–578

Braun N, Michel U, Ernst BP *et al* 1996 Gene polymorphism at position -308 of the tumor necrosis factor-alpha (TNF-α) in multiple sclerosis and its influence on the regulation of TNF-α production. *Neurosci Lett* **215**: 75–78

Brautbar C, Alter M, Kahana E 1976 HLA antigens in multiple sclerosis. *Neurology* **26**: 50–56

Bregman BS, Kunkel-Bagden E, Schnell L *et al* 1995 Recovery from spinal cord injury mediated by antibodies to neurite growth inhibitors. *Nature* **378**: 498–501

Brehm U, Piddlesden SJ, Gardinier MV, Linington C 1999 Epitope specificity of demyelinating monoclonal autoantibodies directed against the human myelin oligodendrocyte glycoprotein (MOG). *J Neuroimmunol* **97**: 9–15

Breij ECW, van der Pol W-L, van Winsen L *et al* 2003 No association of FcγRIIa, FcγRIIIa and FCγRIIIb polymorphisms with MS. *J Neuroimmunol* **140**: 210–215

Breithaupt C, Schubart A, Zander H *et al* 2003 Structural insights into the antigenicity of myelin oligodendrocyte glycoprotein. *Proc Natl Acad Sci USA* **100**: 9446–9451

Breland AE, Currier RD 1983 Scorpion venom and multiple sclerosis. *Lancet* **ii**: 1021

Brenner RE, Munro PM, Williams SC *et al* 1993 The proton NMR spectrum in acute EAE: the significance of the change in the Cho:Cr ratio. *Magn Reson Med* **29**: 737–745

Brenner T, Arnon R, Sela M *et al* 2001 Humoral and cellular immune responses to Copolymer 1 in multiple sclerosis patients treated with Copaxone. *J Neuroimmunol* **115**: 152–160

Brewis M, Poskanzer DC, Rolland C, Miller H 1966 Neurological disease in an English city. *Acta Neurol Scand* **42 (Suppl 24)**: 1–89

Brex PA, Jenkins R, Fox NC *et al* 2000 Detection of ventricular enlargement in patients at the earliest clinical stage of MS. *Neurology* **54**: 1689–1691

Brex PA, Miszkiel KA, O'Riordan JI *et al* 2001a Assessing the risk of early multiple sclerosis in patients with clinically isolated syndromes: the role of a follow up MRI. *J Neurol Neurosurg Psychiatry* **70**: 390–393

Brex PA, Molyneux PD, Smiddy P *et al* 2001b The effect of interferon beta-1b on the size and evolution of enhancing lesions in secondary progressive MS. *Neurology* **57**: 2185–2190

Brex PA, Ciccarelli O, O'Riordan JI *et al* 2002 A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med* **346**: 158–164

Brey RL, Holliday SL, Saklad AR *et al* 2002 Neuropsychiatric syndromes in lupus: prevalence using standardised definitions. *Neurology* **58**: 1214–1220

Briant L, Avoustin P, Clayton J *et al* 1993 Multiple sclerosis susceptibility: population and twin study of polymorphisms in the T cell receptor beta and gamma genes region. French Group on Multiple Sclerosis. *Autoimmunity* **15**: 67–73

Brickner RM 1935 Quinine therapy in cases of multiple sclerosis over a five year period. *Arch Neurol Psychiatry* **33**: 1235–1254

Brickner RM 1936 A critique of therapy in multiple sclerosis. *Bull Neurol Inst NY* **4**: 665–698

Brickner RM 1950 The significance of localised vasoconstrictions in multiple sclerosis. *Res Publ Assoc Res Nerv Mental Dis* **28**: 236–244

Brierley CM, Crang AJ, Iwashita Y *et al* 2001 Remyelination of demyelinated CNS axons by transplanted human Schwann cells: the deleterious effect of contaminating fibroblasts. *Cell Transplant* **10**: 305–315

Brightman M 1991 Implication of astroglia in the blood-brain barrier. *Ann NY Acad Sci* **633**: 343–347

Bril V, Ilse WK, Pearce R *et al* 1996 Pilot trial of immunoglobulin versus plasma exchange in patients with Guillain-Barre syndrome. *Neurology* **46**: 100–103

Brindley GS 1994 Impotence and ejaculatory failure. *The Handbook of Neuro-Urology*. New York, Dekker: pp. 31–348

Brindley GS 1970 *Physiology of the Retina and Visual Pathway*. London, Edward Arnold

Brindley GS, Polkey CE, Rushton DN 1982 Sacral anterior root stimulation for bladder control in paraplegia. *Paraplegia* **20**: 365–381

Brink BP, Veerhuis R, Breij EC *et al* 2005 The pathology of multiple sclerosis is location dependent: no significant complement activation is detected in purely cortical lesions. *J Neuropathol Exp Neurol* **64**: 147–155

Brinkmeier H, Wollinsky KH, Seewald MJ *et al* 1993 Factors in the cerebrospinal fluid of multiple sclerosis patients interfering with voltage-dependent sodium channels. *Neurosci Lett* **156**: 172–175

Brinkmeier H, Seewald MJ, Wollinsky KH, Rudel R 1996 On the nature of endogenous antiexcitatory factors in the cerebrospinal fluid of patients with demyelinating neurological disease. *Muscle Nerve* **19**: 54–62

Brinkmeier H, Aulkemeyer P, Wollinsky KH, Rudel R 2000 An endogenous pentapeptide acting as a sodium channel blocker in inflammatory autoimmune disorders of the central nervous system. *Nature Med* **6**: 808–811

Brisman R, Mooij R 2000 Gamma knife radiosurgery for trigeminal neuralgia: dose-volume histograms of the brainstem and trigeminal nerve. *J Neurosurg* **93**: 155–158

Brismar T 1981a Electrical properties of isolated demyelinated rat nerve fibres. *Acta Physiol Scand* **113**: 161–166

Brismar T 1981b Specific permeability properties of demyelinated rat nerve fibres. *Acta Physiol Scand* **113**: 167–176

Brismar T, Frankenhaeuser B 1981 Potential clamp analysis of mammalian myelinated fibres. *Trends Neurosci* **4**: 68–70

Britton CB, Meas-Tejada R, Fenoglio CM, Hays AP, Garvey GG, Miller JR 1985 A new complication of AIDS: thoracic myelitis caused by herpes simplex virus. *Neurology* **35**: 1071–1074

British and Dutch Multiple Sclerosis Azathioprine Trial Group 1988a Histocompatibility antigens in multiple sclerosis patients participating in a multicentre trial of azathioprine. *J Neurol Neurosurg Psychiatry* **51**: 412–415

British and Dutch Multiple Sclerosis Azathioprine Trial Group 1988b Double masked trial of azathioprine in multiple sclerosis. *Lancet* **ii**: 179–183

Broadley SA, Deans J, Sawcer SJ *et al* 2000 Autoimmune disease in first degree relatives of patients with multiple sclerosis in the United Kingdom. *Brain* **123**: 1102–1111

Broadley SA, Sawcer S, D'Alfonso S *et al* 2001a A genome screen for multiple sclerosis in Italian families. *Genes Immun* **2**: 205–210

Broadley SA, Sawcer SJ, Chataway SJ *et al* 2001b No association between multiple sclerosis and the notch3 gene responsible for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *J Neurol Neurosurg Psychiatry* **71**: 97–99

Broadwell RD, Salcman M 1981 Expanding the definition of the blood-brain barrier to protein. *Proc Natl Acad Sci USA* **78**: 7820–7824

Brocke S, Gaur A, Piercy C *et al* 1993 Induction of relapsing paralysis in experimental autoimmune encephalomyelitis by bacterial superantigen. *Nature* **365**: 642–644

Brocke S, Piercy C, Steinman L *et al* 1999 Antibodies to CD44 and integrin α4, but not L-selectin, prevent central nervous system inflammation and experimental encephalomyelitis by blocking secondary leukocyte recruitment. *Proc Natl Acad Sci USA* **96**: 6896–6901

Brockmann K, Dechent P, Wilken B *et al* 2003 Proton MRS profile of cerebral metabolic abnormalities in Krabbe disease. *Neurology* **60**: 819–825

Brod SA, Marshall GD, Henninger EM *et al* 1996 Interferon-β1b treatment decreases tumor necrosis factor-α and increases interleukin-6 production in multiple sclerosis. *Neurology* **46**: 1633–1638

Brod SA, Lindsey JW, Vriesendorp FS *et al* 2001 Ingested IFN-alpha: results of a pilot study in relapsing–remitting MS. *Neurology* **57**: 845–852

Broggi G, Ferroli P, Franzini A *et al* 2000 Microvascular decompression for trigeminal neuralgia: comments on a series of 250 cases, including 10 patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **68**: 59–64

Broholm H, Andersen B, Wanscher B *et al* 2004 Nitric oxide synthase expression and enzymatic activity in multiple sclerosis. *Acta Neurol Scand* **109**: 261–269

Broman T 1964 Blood brain barrier damage in multiple sclerosis. Supra-vital test observations. *Acta Neurol Scand* **10**: 21–24

Broman T, Bergmann L, Fog T *et al* 1965 Aspects of classification methods in multiple sclerosis. *Acta Neurol Scand* **41 (Suppl 13)**: 543–548

Broman T, Andersen O, Bergmann L 1981 Clinical studies on multiple sclerosis. I. Presentation of an incidence material from Gothenburg. *Acta Neurol Scand* **63**: 6–33

Brønnum-Hansen H, Koch-Henriksen N, Hyllested K 1994 Survival of patients with multiple sclerosis in Denmark: a nationwide, long term epidemiologic survey. *Neurology* **44**: 1901–1907

Brønnum-Hansen H, Koch-Henriksen N, Stenager E 2004 Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain* **127**: 844–850

Bronstein AM, Morris J, du Boulay GH *et al* 1990a Abnormalities of horizontal gaze: clinical oculographic and magnetic resonance imaging findings. I. Abducens palsy. *J Neurol Neurosurg Psychiatry* **53**: 194–199

Bronstein AM, Rudge P, Morris P *et al* 1990b Abnormalities of horizontal gaze: clinical oculographic and magnetic resonance imaging findings. II. Gaze palsy and internuclear ophthalmoplegia. *J Neurol Neurosurg Psychiatry* **53**: 200–207

Bronstein JM, Popper P, Micevych PE, Farber DB 1996 Isolation and characterisation of a novel oligodendrocyte-specific protein. *Neurology* **47**: 772–778

Brooks DJ, Leenders KL, Head G *et al* 1984 Studies on regional oxygen utilisation and cognitive function in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **47**: 1182–1191

Brophy B 1987 *Baroque-n'-Roll*. London: Hamilton, pp. 1–27

Brorson JR, Schumacker PT, Zhang H 1999 Nitric oxide acutely inhibits neuronal energy production. *J Neurosci* **19**: 147–158

Brorson O, Brorson SH, Henriksen TH *et al* 2001 Association between multiple sclerosis and cystic structures in cerebrospinal fluid. *Infection* **29**: 315–319

Brosnan CF, Raine CS 1996 Mechanisms of immune injury in multiple sclerosis. *Brain Pathol* **6**: 243–257

Brosnan CF, Stoner GL, Bloom BR, Wisniewski HM 1977 Studies on demyelination by activated lymphocytes in the rabbit eye. II. Antibody dependent cell mediated demyelination. *J Immunol* **118**: 2103–2110

Brosnan CF, Cammer W, Norton WT, Bloom BR 1980 Proteinase inhibitors suppress the development of experimental allergic encephalomyelitis. *Nature* **285**: 235–237

Brosnan CF, Bornstein MB, Bloom BR 1981 The effects of macrophage depletion on the clinical and pathologic expression of experimental allergic encephalomyelitis. *J Immunol* **126**: 614–620

Brosnan CF, Litwak MS, Schroeder CE *et al* 1989 Preliminary studies of cytokine-induced functional effects on the visual pathways in the rabbit. *J Neuroimmunol* **25**: 227–239

Brown AM, Westenbroek RE, Catterall WA, Ransom BR 2001 Axonal L-type Ca2+ channels and anoxic injury in rat CNS white matter. *J Neurophysiology* **85**: 900–911

Brown DL, Login IS, Borish L, Powers PL 2001 An urticarial IgE-mediated reaction to interferon beta-1b. *Neurology* **56**: 1416–1417

Brown GC 1999 Nitric oxide and mitochondrial respiration. *Biochim Biophys Acta* **1411**: 351–369

Brown GC, Borutaite V 2001 Nitric oxide, mitochondria, and cell death. *IUBMB Life* **52**: 189–195

Brown GC, Bolanos JP, Heales SJ, Clark JB 1995 Nitric oxide produced by activated astrocytes rapidly and reversibly inhibits cellular respiration. *Neurosci Lett* **193**: 201–204

Brown J, Jardetzky T, Saper M *et al* 1993 Three dimensional structure of the human class II histocompatibility antigen. *Nature* **332**: 845–850

Brown JR, Beebe GW, Kurtzke JF *et al* 1979 The design of clinical studies to assess therapeutic efficacy in multiple sclerosis. *Neurology* **29**: 3–23

Brown MM, Swash M 1989 Polyarteritis nodosa and other systemic vasculitides. In: Toole JF (ed.) *Handbook of Clinical Neurology*. Amsterdam: Elsevier, Vol. 55 (part III), pp. 353–367

Brown P 1994 Pathophysiology of spasticity. *J Neurol Neurosurg Psychiatry* **57**: 773–777

Brown WF, Ebers GC, Hudson AJ, Pringle CE, Veitch J 1992 Motor evoked responses in primary lateral sclerosis. *Muscle Nerve* **15**: 626–629

Brown WJ 1978 The capillaries in acute and subacute multiple sclerosis plaques: a morphometric analysis. *Neurology* **28**: 84–92

Brownell B, Hughes JT 1962 The distribution of plaques in the cerebrum in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **25**: 315–320

Bruce AJ, Boling W, Kindy MS *et al* 1996 Altered neuronal and microglial responses to excitotoxic and ischemic brain injury in mice lacking TNF receptors. *Nature Med* 2: 788–794

Brück W, Schmied M, Suchanek G *et al* 1994 Oligodendrocytes in the early course of multiple sclerosis. *Ann Neurol* **35**: 65–73

Brück W, Porada P, Poser S *et al* 1995 Monocyte/macrophage differentiation in early multiple sclerosis lesions. *Ann Neurol* **38**: 788–796

Brück W, Bitsch A, Kolenda H *et al* 1997 Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology. *Ann Neurol* **42**: 783–793

Brück W, Lucchinetti CF, Lassmann H 2003 The pathology of primary progressive multiple sclerosis. *Mult Scler* **8**: 93–97

Brumlik J, Means ED 1969 Tremorine-tremor, shivering and acute cerebellar ataxia in the adult and child – a comparative study. *Brain* **92**: 157–190

Brundin L, Morcos E, Olsson T *et al* 1999 Increased intrathecal nitric oxide formation in multiple sclerosis: cerebrospinal fluid nitrite as activity marker. *Eur J Neurol* **6**: 585–590

Brundula V, Rewcastle NB, Metz LM *et al* 2002 Targeting leukocyte MMPs and transmigration: minocycline as a potential therapy for multiple sclerosis. *Brain* **125**: 1297–1308

Brunner C, Lassmann H, Waehneldt TV *et al* 1989 Differential ultrastructural localization of myelin basic protein, myelin/oligodendroglial glycoprotein, and 2',3'-cyclic nucleotide 3'-phosphodiesterase in the CNS of adult rats. *J Neurochem* **52**: 296–304

Brusa A, Jones SJ, Plant GT 2001 Long term remyelination after optic neuritis: a 2 year visual evoked potential and psychophysical serial study. *Brain* **124**: 468–479

Brustle O, Spiro AC, Karram K *et al* 1997 In vitro-generated neural precursors participate in mammalian brain development. *Proc Natl Acad Sci USA* **94**: 14809–14814

Brustle O, Jones KN, Learish RD *et al* 1999 Embryonic stem cell-derived glial precursors: a source of myelinating transplants. *Science* **285**: 754–756

Bsibsi M, Ravid R, Gveric D, van Noort JM 2003 Broad expression of Toll-like receptors in the human central nervous system. *J Neuropathol Exp Neurol* **61**: 1013–1021

Buchanan RJ, Martin RA, Zuniga M *et al* 2004 Nursing home residents with multiple sclerosis: comparisons of African American residents to white residents at admission. *Mult Scler* **10**: 660–667

Buckley C, Kennard C, Swash M 1982 Treatment of acute exacerbations of multiple sclerosis with intravenous methylprednisolone. *J Neurol Neurosurg Psychiatry* **45**: 179–180

Buddeberg BS, Kerschensteiner M, Merkler D *et al* 2004 Behavioural testing in a localised animal model of multiple sclerosis. *J Neuroimmunol* **153**: 158–170

von Büdingen H-C, Tanuma N, Villoslada P *et al* 2001 Immune responses against the myelin/oligodendrocyte glycoprotein in experimental autoimmune demyelination. *J Clin Immunol* **21**: 155–170

von Büdingen HC, Hauser SL, Fuhrmann A *et al* 2002 Molecular characterization of antibody specificities against myelin/oligodendrocyte glycoprotein in autoimmune demyelination. *Proc Natl Acad Sci USA* **99**: 8207–8212

Bufill E, Blesa R, Galan I, Dean G 1995 Prevalence of multiple sclerosis in the region of Osano, Catalonia, northern Spain. *J Neurol Neurosurg Psychiatry* **58**: 577–581

Buhler MMcW, Bennetts BH, Heard RNS, Stewart GJ 2000 T cell receptor β chain genotyping in Australian relapsing–remitting multiple sclerosis patients. *Mult Scler* **6**: 140–147

Buhmann C, Gbadomosi J, Heeson C 2002 Visual recovery in a man with the rare combination of mtDNA 11778 LHON mutation and a MS-like disease after mitoxantrone therapy. *Acta Neurol Scand* **196**: 236–239

Buljevac D, Flach HZ, Hop WCJ *et al* 2002 Prospective study on the relationship between infections and multiple sclerosis exacerbations. *Brain* **125**: 952–960

Buljevac D, Verkooyen RP, Jacobs BC *et al* 2003a *Chlamydia pneumoniae* and the risk for exacerbation in multiple sclerosis patients. *Ann Neurol* **54**: 828–831

Buljevac D, Hop WC, Reedeker W *et al* 2003b Self-reported stressful life events and exacerbations in multiple sclerosis: prospective study. *Brit Med J* **327**: 646

Bulman DE, Ebers GC 1992 The geography of multiple sclerosis reflects genetic susceptibility. *J Trop Geogr Neurol* **2**: 66–72

Bulman DE, Sadovnick AD, Cripps J, Ebers GC 1991a Age of onset in siblings concordant for multiple sclerosis. *Brain* **114**: 937–950

Bulman DE, Armstrong H, Ebers GC 1991b Allele frequencies of the third component of complement (C3) in MS patients. *J Neurol Neurosurg Psychiatry* **54**: 554–555

Bundey S 1991 Uses and limitations of twin studies. *J Neurol* **238**: 360–364

Bunge MB, Bunge RP, Ris H 1961 Ultrastructural study of remyelination in an experimental lesion in adult cat spinal cord. *J Biophys Biochem Cytol* **10**: 67–94

Bunge MB, Bunge RP, Pappas GD 1962 Electron microscopic demonstration of connections between glia and myelin sheaths in the developing mammalian central nervous system. *J Cell Biol* **12**: 448–453

Burchiel KJ 1980 Abnormal impulse generation in focally demyelinated trigeminal roots. *J Neurosurg* **53**:674–683

Burchiel KJ 1981 Ectopic impulse generation in demyelinated axons: effects of Pa_{CO2}, pH, and disodium edetate. *Ann Neurol* **9**: 378–383

Bureau JF, Montagutelli X, Bihl F *et al* 1993 Mapping loci influencing the persistence of Theiler's virus in the murine central nervous system. *Nature Genet* **5**: 87–91

Burgerman R, Rigamonti D, Randle JM, Fishman P, Panitch HS, Johnson KP 1992 The association of cervical spondylosis and multiple sclerosis. *Surg Neurol* **38**: 265–270

Burguera JA, Catalá J, Casanova B 1991 Thalamic demyelination and paroxysmal dystonia in multiple sclerosis. *Mov Disord* **6**: 379–381

Burk K, Abele M, Fetter M *et al* 1996 Autosomal dominant cerebellar ataxia type 1 clinical features and MRI in families with SCA1, SCA2 and SCA3. *Brain* **119**: 1497–1505

Burke D 1993 Microneurography, impulse conduction, and paresthesias. *Muscle Nerve* **16**: 1025–1032

Burke D, Mogyoros I, Vagg R, Kiernan MC 1998 Quantitative description of the voltage dependence of axonal excitability in human cutaneous afferents. *Brain* **121**: 1975–1983

Burke D, Kiernan MC, Bostock H 2001 Excitability of human axons. *Clin Neurophysiol* **112**: 1575–1585

Burne J, Staple JK, Raff MC 1996 Glial cells are increased proportionally in transgenic optic nerves with increased numbers of axons. *J Neurosci* **16**: 2064–2073

Burnet FM 1959 *The Clonal Selection Theory of Acquired Immunity*. Cambridge: Cambridge University Press

Burnfield A 1985 *Multiple Sclerosis: A Personal Exploration*. London: Souvenir Press

Burnham JA, Wright RP, Driesbach J, Murray RS 1991 The effect of high-dose steroids on MRI gadolinium enhancement in acute demyelinating lesions. *Neurology* **41**: 1349–1354

Burns FR, Li X, Shen N *et al* 1989 Both rat and mouse T cell receptors specific for the encephalitogenic determinant of myelin basic protein use similar Vα and Vβ chain genes even though the major histocompatibility complex and encephalitogenic determinants being recognized are different. *J Exp Med* **169**: 27–39

Burns J, Rosenzweig A, Zweiman B, Lisak RP 1983 Isolation of myelin basic protein-reactive T cell lines from normal human blood. *Cell Immunol* **81**: 435–440

Burns J, Littlefield K, Gill J, Trotter J 1991 Autoantigen-induced self lysis of human myelin basic protein-specific T lymphocytes. *J Neuroimmunol* **35**: 227–236

Burt R 1997 BMT for severe autoimmune diseases: an idea whose time has come. *Oncology* **11**: 1001–1017

Burt R, Burns W, Hess A 1995 Bone marrow transplantation for multiple sclerosis. *Bone Marrow Transplant* **16**: 1–6

Burt RK, Burns WH, Miller SD 1997 Bone marrow transplantation for multiple sclerosis: returning to Pandora's box. *Immunol Today* **18**: 559–561

Burt RK, Cohen BA, Russell E *et al* 2003 Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. *Blood* **102**: 2373–2378

Burt RK, Cohen B, Rose J *et al* 2005 Hematopoietic stem cell transplantation for multiple sclerosis. *Arch Neurol* **62**: 860–864

Burwick RM, Ramsay PP, Haines JL *et al* 2005 *APOE* in multiple sclerosis susceptibility and severity: meta- and pooled analyses (submitted)

Bush TG, Puvanachandra N, Horner CH *et al* 1999 Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. *Neuron* **23**: 297–308

Butcher EC, Picker LJ 1996 Lymphocyte homing and homeostasis. *Science* **272**: 60–66

Butt AM, Jenkins HG 1994 Morphological changes in oligodendrocytes in the intact mouse optic nerve following intravitreal injection of tumour necrosis factor. *J Neuroimmunol* **51**: 27–33

Butt AM, Ransom BR 1989 Visualisation of oligodendrocytes and astrocytes in the intact rat optic nerve by intracellular injection of lucifer yellow and horseradish peroxidase. *Glia* **2**: 470–475

Butt AM, Duncan A, Hornby MF *et al* 1999 Cells expressing the NG2 antigen contact nodes of Ranvier in adult CNS white matter. *Glia* **26**: 84–91

Butt AM, Kiff J, Hubbard P, Berry M 2002 Synantocytes: new functions for novel NG2 expressing glia. *J Neurocytol* **31**: 551–565

Butter C, Baker D, O'Neill JK, Turk JL 1991 Mononuclear cell trafficking and plasma protein extravasation into the CNS during chronic relapsing experimental allergic encephalomyelitis in Biozzi AB/H mice. *J Neurol Sci* **104**: 9–12

Butterfield RJ, Sudweeks JD, Blakenhorn EP *et al* 1998 New genetic loci that control susceptibility and symptoms of experimental allergic encephalomyelitis in inbred mice. *J Immunol* **161**: 1860–1867

Butterfield RJ, Blankenhorn LP, Roper RJ *et al* 1999 Genetic analysis of disease subtypes and sexual dimorphisms in mouse experimental allergic encephalomyelitis (EAE): relapsing/remitting and monophasic remitting/nonrelapsing EAE are immunogenetically distinct. *J Immunol* **162**: 3096–3102

Butterfield RJ, Blankenhorn EP, Roper RJ *et al* 2000 Identification of genetic loci controlling the characteristics and severity of brain and spinal cord lesions in experimental allergic encephalomyelitis. *Am J Pathol* **157**: 637–645

Butzkueven H, Zhang JG, Soilu-Hanninen M *et al* 2002 LIF receptor signaling limits immune-mediated demyelination by enhancing oligodendrocyte survival. *Nature Med* **8**: 613–619

Bye AME, Kendall B, Wilson J 1985 Multiple sclerosis in childhood: a new look. *Dev Med Child Neurol* **27**: 215–222

Cabarrocas J, Bauer J, Piaggio E *et al* 2003 Effective and selective immune surveillance of the brain by MHC class I-restricted cytotoxic T lymphocytes. *Eur J Immunol* **33**: 1174–1182

Cabre P, Heinzlef O, Merle H *et al* 2001 MS and neuromyelitis optica in Martinique (French West Indies). *Neurology* **56**: 507–514

Cabre P, Signate A, Olindo S *et al* 2005 Role of return migration in the emergence of multiple sclerosis in the French West Indies. *Brain* [epub ahead of print]

Cabrera-Gomez JA, Echazabal-Santana N, Real-Gonzalez Y *et al* 2005 Hereditary Melkersson–Rosenthal syndrome and multiple sclerosis. *Mult Scler* **11**: 364–366

Cai D, Shen Y, De Bellard M *et al* 1999 Prior exposure to neurotrophins blocks inhibition of axonal regeneration by MAG and myelin via a cAMP-dependent mechanism. *Neuron* **22**: 89–101

Caillier S, Barcellos LF, Baranzini SE *et al* 2003 Osteopontin polymorphisms and disease course in multiple sclerosis. *Genes Immun* **4**: 312–315

Caine ED, Schwid SR 2002 Multiple sclerosis, depression, and the risk of suicide. *Neurology* **59**: 662–663

Cajal SR 1894 *Les nouvelles ideés sur la structure du système nerveux*. Paris: Reinwald

Cajal SR 1899–1904 *Textura del sistema nervioso del hombre y de los vertebrados*. 3 volumes. Madrid 1899–1904 [*Texture of the Nervous System of Man and Vertebrates*, Pasik P, Pasik T (trans.), Vienna: Springer, 1999–2002]

Cajal SR 1913 Contribucion al conocmiento de la neuroglia del cerebra humano. *Trab Lab de Invest Biol* **11**: 255–315

Cala LA, Mastaglia FL 1976 Computerised axial tomography in multiple sclerosis. *Lancet* **i**: 689

Calabrese V, Bella R, Testa D *et al* 1998 Increased cerebrospinal fluid and plasma levels of ultraweak chemiluminescence are associated with changes in the thiol pool and lipid-soluble fluorescence in multiple sclerosis: the pathogenic role of oxidative stress. *Drugs Exp Clin Res* **24**: 125–131

Calabrese V, Scapagnini G, Ravagna A *et al* 2002 Nitric oxide synthase is present in the cerebrospinal fluid of patients with active multiple sclerosis and is associated with increases in cerebrospinal fluid protein nitrotyrosine and S-nitrosothiols and with changes in glutathione levels. *J Neurosci Res* **70**: 580–587

Calabresi PA, Pelfrey CM, Tranquill LR *et al* 1997a VLA-4 expression on peripheral blood lymphocytes is downregulated after treatment of multiple sclerosis with interferon beta. *Neurology* **49**: 1111–1116

Calabresi PA, Stone LA, Bash CN *et al* 1997b Interferon beta results in immediate reduction of contrast-enhanced MRI lesions in multiple sclerosis patients followed by weekly MRI. *Neurology* **48**: 1446–1448

Calabresi PA, Tranquill LR, Dambrosia JM *et al* 1997c Increases in soluble VCAM-1 correlate with a decrease in MRI lesions in multiple sclerosis treated with interferon beta-1b. *Ann Neurol* **41**: 669–674

Calabresi PA, Austin H, Racke MK *et al* 2002a Impaired renal function in progressive multiple sclerosis. *Neurology* **59**:1799–1801

Calabresi PA, Wilterdink JL, Rogg JM *et al* 2002b An open-label trial of combination therapy with interferon beta-1a and oral methotrexate in MS. *Neurology* **58**: 314–317

Calaora V, Rogister B, Bismuth K *et al* 2001 Neuregulin signaling regulates neural precursor growth and the generation of oligodendrocytes in vitro. *J Neurosci* **21**: 4740–4751

Calcagno P, Ruoppolo G, Grasso MG *et al* 2002 Dysphagia in multiple sclerosis – prevalence and prognostic factors. *Acta Neurol Scand* **105**: 40–43

Caldwell JH, Schaller KL, Lasher RS *et al* 2000 Sodium channel Na(v)1.6 is localized at nodes of Ranvier, dendrites, and synapses. *Proc Natl Acad Sci USA* **97**: 5616–5620

Callanan MM, Logsdail SJ, Ron MA, Warrington EK 1989 Cognitive impairment in patients with clinically isolated lesions of the type seen in multiple sclerosis. *Brain* **1123**: 361–374

Callegaro D, de Lolio CA, Radvany J *et al* 1992 Prevalence of multiple sclerosis in the city of Sao Paolo, Brazil in 1990. *Neuroepidemiology* **11**: 11–14

Callegaro D, Goldbaum M, Morais L *et al* 2001 The prevalence of multiple sclerosis in the city of Sao Paulo, Brazil 1997. *Acta Neurol Scand* **104**: 208–213

Calvin WH, Loeser JD, Howe JF 1977 A neurophysiological theory for the pain mechanism of tic douloureux. *Pain* **3**: 147–154

Calvin WH, Devor M, Howe JF 1982 Can neuralgias arise from minor demyelination? Spontaneous firing, mechanosensitivity, and after discharge from conducting axons. *Exp Neurol* **75**: 755–763

Calza L, Fernandez M, Giuliani A *et al* 2002 Thyroid hormone activates oligodendrocyte precursors and increases a myelin-forming protein and NGF content in the spinal cord during experimental allergic encephalo-myelitis. *Proc Natl Acad Sci USA* **99**: 3258–3263

Camenga DL, Johnson KP, Alter M *et al* 1986 Systemic recombinant α-2 therapy in relapsing multiple sclerosis. *Arch Neurol* **43**: 1239–1246

Cameron RS, Rakic P 1991 Glial cell lineage in the cerebral cortex: a review and synthesis. *Glia* 4: 124–137

Cammer W 2002 Apoptosis of oligodendrocytes in secondary cultures from neonatal rat brains. *Neurosci Lett* **327**: 123–127

Cammer W, Zhang H 1999 Maturation of oligodendrocytes is more sensitive to TNFα than is survival of precursors and immature oligodendrocytes. *J Neuroimmunol* **97**: 37–42

Camp SJ, Stevenson VL, Thompson AJ *et al* 1999 Cognitive function in primary progressive and transitional progressive multiple sclerosis: a controlled study with MRI correlates. *Brain* **122**: 1341–1348

Campbell AMG, Daniel P, Porter RJ *et al* 1947 Disease of the nervous system occurring among research workers on swayback in lambs. *Brain* **70**: 50–58

Campbell AMG, Herdan G, Tatlow WF, Whittle EG 1950 Lead in relation to disseminated sclerosis. *Brain* **73**: 52–70

Campbell IL, Stalder AK, Akwa Y *et al* 1998 Transgenic models to study the actions of cytokines in the central nervous system. *Neuroimmunomodulation* 5: 126–135

Campi A, Filippi M, Comi G *et al* 1995 Acute transverse myelopathy: spinal and cranial MR study with clinical follow-up. *Am J Neuroradiol* **16**: 115–123

Campi A, Benndorf G, Filippi M *et al* 2001 Primary angiitis of the central nervous system: serial MRI of brain and spinal cord. *Neuroradiology* **43**: 599–607

Campuzano V, Montermini L, Molto MD *et al* 1996 Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* **271**: 1423–1427

Canadian Burden of Illness Study Group 1998 Burden of illness of multiple sclerosis. Part I: Cost of illness. *Can J Neurol Sci* **25**: 23–30

Canadian Co-operative Multiple Sclerosis Study Group 1991 The Canadian co-operative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. *Lancet* **337**: 441–446

Canadian MS Research Group 1987 A randomised controlled trial of amantidine in fatigue associated with multiple sclerosis. *Can J Neurol Sci* **14**: 273–278

Cangemi FE, Bergen RL 1980 Optic atrophy following swine flu vaccination. *Ann Ophthalmol* **12**: 857–863

Cannella B, Raine CS 1995 The adhesion molecule and cytokine profile of multiple sclerosis lesions. *Ann Neurol* **37**: 424–435

Cannella B, Raine CS 2004 Multiple sclerosis: cytokine receptors on oligodendrocytes predict innate regulation. *Ann Neurol* **55**: 46–57

Cannella B, Cross AH, Raine CS 1991 Adhesion-related molecules in the central nervous system. Upregulation correlates with inflammatory cell influx during relapsing experimental autoimmune encephalomyelitis. *Lab Invest* **65**: 23–31

Cannella B, Hoban CJ, Gao YL *et al* 1998 The neuregulin, glial growth factor 2, diminishes autoimmune demyelination and enhances remyelination in a chronic relapsing model for multiple sclerosis. *Proc Natl Acad Sci USA* **95**: 10100–10105

Cannella B, Pitt D, Marchionni M, Raine CS 1999 Neuregulin and erbB receptor expression in normal and diseased human

white matter. *J Neuroimmunol* **100**: 233–242
Cannella B, Pitt D, Capello E, Raine CS 2000 Insulin-like growth factor-1 fails to enhance central nervous system meylin repair during autoimmune demyelination. *Am J Pathol* **157**: 933–943
Canoll PD, Musacchia JM, Hardy R *et al* 1996 GGF/neuregulin is a neuronal signal that promotes the proliferation and survival and inhibits the differentiation of oligodendrocyte progenitors. *Neuron* **17**: 229–243
Cao L, Liu L, Chen ZY *et al* 2004 Olfactory ensheathing cells genetically modified to secrete GDNF to promote spinal cord repair. *Brain* **127**: 535–549
Caplan LR, Nadelson T 1980 Multiple sclerosis and hysteria: lessons learnt from their association. *J Am Med Assoc* **243**: 2418–2420
Cappelen-Smith C, Kuwabara S, Lin CSY *et al* 2000 Activity-dependent hyperpolarization and conduction block in chronic inflammatory demyelinating polyneuropathy. *Ann Neurol* **48**: 826–832
Caraccio N, Dardano A, Manfredonia F *et al* 2005 Long-term follow-up of 106 multiple sclerosis patients undergoing IFN-β1a or 1b therapy: predictive factors of thyroid disease development and duration. *J Clin Endocrinol Metab* **90**: 4133–4137
Caramalho I, Lopes-Carvalho T, Ostler D *et al* 2003 Regulatory T cells selectively express Toll-like receptors and are activated by lipopolysaccharide. *J Exp Med* **197**: 403–411
Caramanos Z, Arnold DL 2005 Evidence for use of glatiramer acetate in multiple sclerosis. *Lancet Neurol* **4**: 74–75; discussion 76–77
Carboni S, Aboul-Enein F, Waltzinger C *et al* 2003 CD134 plays a crucial role in the pathogenesis of EAE and is upregulated in the CNS of patients with multiple sclerosis. *J Neuroimmunol* **145**: 1–11
Cardon T, Wyremblewski P, Lesoin F, Brunaud V, Destée A 1992 Angiome caverneux de la moelle cervicale. *Rev Neurol* **148**: 152–154
Carey RG, Seibert JH, Posavac EJ 1988 Who makes the most progress in inpatient rehabilitation? An analysis of functional gain. *Arch Phys Med Rehab* **69**: 337–343
Carlander B, Dauvilliers Y, Billiard M 2001 Immunological aspects of narcolepsy. *Rev Neurol* **157**: S97–S100
Carlson CS, Eberle M, Kruglyak L, Nickerson D 2004 Mapping complex disease loci in whole-genome association studies. *Nature* **429**: 446–452
Carmichael EA 1931 The aetiology of disseminated sclerosis: some criticisms of recent work, especially to the 'spherula insularis'. *Proc R Soc Med* **34**: 591–606
Carmody RJ, Hilliard B, Maguschak K *et al* 2002 Genomic scale profiling of autoimmune inflammation in the central nervous system: the nervous response to inflammation. *J Neuroimmunol* **133**: 95–107
Caroll WM, Jennings AR, Ironside LJ 1998 Identification of the adult resting progenitor cell by autoradiographic tracking of oligodendrocyte precursors in experimental CNS demyelination. *Brain* **121**: 293–302
Carp RI, Licursi PC, Merz PA, Merz GS 1972 Decreased percentage of polymorphonuclear neutrophils in mouse peripheral blood after inoculation with material from multiple sclerosis patients. *J Exp Med* **136**: 618–629
Carp RI, Licursi PL, Merz PA *et al* 1977 Multiple sclerosis – associated agent. *Lancet* **ii**: 814
Carrieri PB, Provitera V, De Rosa T *et al* 1998 Profile of cerebrospinal fluid and serum cytokines in patients with relapsing–remitting multiple sclerosis: a correlation with clinical activity. *Immunopharmacol Immun* **20**: 373–382
Carrington M, Colonna M, Spies T *et al* 1993 Haplotypic variation of the transporter associated with antigen processing (TAP) genes and their extension of HLA class II region haplotypes. *Immunogenetics* **37**: 266–273
Carrithers MD, Visintin I, Kang SJ, Janeway CA 2000 Differential adhesion molecule requirements for immune surveillance and inflammatory recruitment. *Brain* **123**: 1092–1101
Carrithers MD, Visintin I, Viret C, Janeway CS Jr 2002 Role of genetic background in P selectin-dependent immune surveillance of the central nervous system. *J Neuroimmunol* **129**: 51–57
Carrizosa AM, Nicholson LB, Farzan M *et al* 1998 Expansion by self antigen is necessary for the induction of experimental autoimmune encephalomyelitis by T cells primed with a cross-reactive environmental antigen. *J Immunol* **161**: 3307–3314
Carroll CB, Zajicek JP 2004 The 'harlequin' sign in association with multiple sclerosis. *J Neurol* **251**: 1145–1146
Carswell R 1838 *Pathological Anatomy: Illustrations of the Elementary Forms of Disease*. London: Orme, Brown, Green & Longman
Carter JL, Noseworthy JH 1994 Ventilatory dysfunction in multiple sclerosis. *Clin Chest Med* **15**: 693–703
Carter S, Sciarra D, Merritt HH 1950 The course of multiple sclerosis as determined by autopsy proven cases. *Res Publ Assoc Res Nerv Mental Dis* **28**: 471–511
Cartlidge NEF 1972 Autonomic function in multiple sclerosis. *Brain* **95**: 661–664
Cartlidge NEF, Hudgson P, Weightman D 1974 A comparison of baclofen and diazepam in the treatment of spasticity. *J Neurol Sci* **23**: 17–24
Carton H, Vlietinck R, Debruyne J *et al* 1997 Recurrence risks of multiple sclerosis in relatives of patients in Flanders, Belgium. *J Neurol Neurosurg Psychiatry* **62**: 329–333
Casaccia-Bonnefil P, Carter BD, Dobrowsky RT, Chao MV 1996 Death of oligodendrocytes mediated by the interaction of nerve growth factor with its receptor p75. *Nature* **383**: 716–719
Cascino I, Galeazzi M, Salvetti M *et al* 1994 HSP70–1 promoter polymorphism tested in three autoimmune diseases. *Immunogenet* **39**: 291–293
Cascino I, Ballerini C, Audino S *et al* 1998 Fas gene polymorphisms are not associated with systemic lupus erythematosus, multiple sclerosis and HIV infection. *Disease Markers* **13**: 221–225
Casellas R, Shih T, Kleinewietfeld M *et al* 2001 Contribution of receptor editing to the antibody repertoire. *Science* **291**: 1541–1544
Cash E, Minty A, Ferrara P *et al* 1994 Macrophage-inactivating IL-13 suppresses experimental autoimmune encephalomyelitis in rats. *J Immunol* **153**: 4258–4267
Casquero P, Villoslada P, Montalban X, Torrent M 2001 Frequency of multiple sclerosis in Menorca, Balearic Islands, Spain. *Neuroepidemiology* **20**: 129–133
Cassetta I, Granieri E, Marchi D *et al* 1998 An epidemiological study of multiple sclerosis in central Sardinia, Italy. *Acta Neurol Scand* **98**: 391–394
Cassetta I, Invernizzi M, Granieir E 2001 Multiple sclerosis and dental amalgam: case-control study in Ferrara, Italy. *Neuroepidemiology* **20**: 134–137
Castaigne P, Escourolle R, Laplane D, Augustin P 1966 Comas transitoires avec hyperthermie au cours de la sclérose en plaques. *Rev Neurol* **114**: 147–150
Castaigne P, Cambier J, Masson M *et al* 1970 Les manifestations motrices paroxystiques de la sclérose en plaques. *Presse Med* **78**: 1921–1924
Castaigne P, Lhermitte F, Escurolle R *et al* 1981 Les scléroses en plaques asymptomatiques. *Rev Neurol* **137**: 729–739
Casula FC (undated) *The History of Sardinia*. Cagliari: Editrice Mediterranea
Caton R 1875 The electric currents of the brain. *Br Med J* **2**: 278
Cattaneo C, Almici C, Borlenghi E *et al* 2003 A case of acute promyelocytic leukaemia following mitoxantrone treatment of multiple sclerosis. *Leukemia* **17**: 985–986
Cavalli-Sforza LL, Menozzi P, Piazza A 1994 *The History and Geography of Human Genes*. Princeton, NJ: Princeton Universty Press
Cecconi F, Alvarez-Bolado G, Meyer BI *et al* 1998 Apaf1 (CED-4 homolog) regulates programmed cell death in mammalian development. *Cell* **94**: 727–737
Celesia GG, Kaufman DI, Brigell M *et al* 1990 Optic neuritis: a prospective study. *Neurology* **40**: 919–923
Celius EG, Vandvik B 2001 Multiple sclerosis in Oslo, Norway: prevalence on 1 January 1995 and incidence over a 25-year period. *Eur J Neurol* **8**: 463–469
Celius EG, Harbo HF, Egeland T *et al* 2000 Sex and age at diagnosis are correlated with the HLA-DR2, DQ6 haplotype in multiple sclerosis. *J Neurol Sci* **178**: 132–135
Cella DF, Dineen K, Arnason B *et al* 1996 Validation of the functional assessment of multiple sclerosis quality of life instrument. *Neurology* **47**: 129–139

Cella M, Jabrossay F, Alebardi O *et al* 1999 Plasmacytoid monocytes migrate to inflamed lymph nodes and produce large amounts of type I interferon. *Nature Med* **5**: 919–923

Ceman S, Rudersdorf R, Long E, Demars R 1992 MHC class II deletion mutant expresses normal levels of transgene encoded class II molecules that have abnormal conformation and impaired antigen presentation ability. *J Immunol* **149**: 754–761

Cendrowski WS 1968 Multiple sclerosis: discordance of three dizygotic twin pairs. *J Med Genet* **5**: 266–268

Cendrowski WS, Makowski J 1972 Epilepsy in multiple sclerosis. *J Neurol Sci* **17**: 389–398

Cendrowski WS, Wender M, Dominik W *et al* 1969 Epidemiological study of multiple sclerosis in Western Poland. *Eur Neurol* **2**: 90–108

Cengiz N, Ozbenli T, Onar L *et al* 2002 Adult metachromatic leukodystrophy: three cases with normal nerve conduction velocities in a family. *Acta Neurol Scand* **105**: 454–457

Centonze D, Rossi S, Boffa L *et al* 2005 CSF from MS patients can induce acute conduction block in the isolated optic nerve. *Eur J Neurol* **12:** 45–48

Cepok S, Jacobsen M, Schock S *et al* 2001 Patterns of cerebrospinal fluid pathology correlate with disease progression in multiple sclerosis. *Brain* **124**: 2169–2176

Cepok S, Rosche B, Grummel V *et al* 2005a Short-lived plasma blasts are the main B cell effector subset during the course of multiple sclerosis. *Brain* **128**: 1667–1676

Cepok S, Zhou D, Srivastava S *et al* 2005b Identification of Epstein–Barr virus proteins as putative targets of the immune response in multiple sclerosis. *J Clin Invest* **115**: 1352–1360

Cercignani M, Bozzali M, Iannucci G *et al* 2001a Magnetisation transfer ratio and mean diffusivity of normal appearing white and grey matter from patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **70**: 311–317

Cercignani M, Inglese M, Pagani E *et al* 2001b Mean diffusivity and fractional anisotropy histograms of patients with multiple sclerosis. *Am J Neuroradiol* **22**: 952–958

Cerf JA, Carels G 1966 Multiple sclerosis: serum factor producing reversible alterations in bioelectric responses. *Science* **152**: 1066–1068

Cerizza M, Nemni R, Tamma F 1987 Adult metachromatic leukodystrophy: an underdiagnosed disease. *J Neurol Neurosurg Psychiatry* **50**: 1710–1712

Cestan R, Guillain G 1900 Le paraplegie spasmodique familiale et la sclérose en plaques familiale. *Rev Med* **20**: 813–836

Chabas D, Baranzini SE, Mitchell D *et al* 2001 The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease. *Science* **294**: 1731–1735

Chabriat H, Chen QM, Poisson M, Delattre JY 1994 Dégénérescence cérébelleuse paranéoplastique. *Rev Neurol* **150**: 105–114

Chagnac Y, Martinovits G, Tadmor R, Goldhammer Y 1986 Paroxysmal atrial fibrillation associated with an attack of multiple sclerosis. *Postgrad Med J* **62**: 385–387

Chajek T, Fainaru M 1975 Behçet's disease: report of 41 cases and review of literature. *Medicine* **54**: 179–196

Chakraborty R, Kamboh, MI, Nwankwo M, Ferrell RE 1992 Caucasian genes in American blacks: new data. *Am J Hum Genet* **50**: 145–155

Chalk JB, McCombe PA, Pender MP 1994 Conduction abnormalities are restricted to the central nervous system in experimental autoimmune encephalomyelitis induced by inoculation with proteolipid protein but not with myelin basic protein. *Brain* **117**: 975–986

Chalk JB, McCombe PA, Pender MP 1995 Restoration of conduction in the spinal roots correlates with clinical recovery from experimental autoimmune encephalomyelitis. *Muscle Nerve* **18**: 1093–1100

Challoner PB, Smith KT, Parker JD *et al* 1995 Plaque-associated expression of human herpesvirus 6 in multiple sclerosis. *Proc Natl Acad Sci USA* **92**: 7440–7444

Chalmers RM, Robertson NP, Kellar-Wood H *et al* 1995 Sequence of the human homologue of a mitochondrially encoded murine transplantation antigen in patients with multiple sclerosis. *J Neurol* **242**: 332–334

Chalmers RM, Robertson NP, Compston DAS, Harding AE 1996 Sequence of mitochondrial DNA in patients with multiple sclerosis. *Ann Neurol* **40**: 239–243

CHAMPS Study Group 2002 MRI predictors of early conversion to clinically definite MS in the CHAMPS placebo group. *Neurology* **59**: 998–1005

Chancellor AM, Addidle M, Dawson K 2003 Multiple sclerosis is more prevalent in northern New Zealand than previously reported. *Intern Med J* **33**: 79–83

Chandler BJ 1999 Impact of neurologic disability on sex and relationships. In: Fowler C (ed.) *Neurology of Bladder, Bowel, and Sexual Dysfunction*. Boston, MA: Butterworth-Heinemann, pp. 69–93

Chandran SC, Svendsen C, Compston A, Scolding N 1998 Regional potential for oligodendrocyte generation in the rodent embryonic spinal cord following exposure to EGF and FGF-2. *Glia* **24**: 382–389

Chandran SC, Kato H, Gerreli D *et al* 2003 FGF dependent generation of oligodendrocytes by a hedgehog independent pathway. *Development* **30**: 6599–6609

Chandran SC, Compston DAS, Jauniaux E *et al* 2004 Differential generation of oligodendrocytes from human and rodent embryonic spinal cord neural precursors. *Glia* **47**: 314–324

Chang A, Nishiyama A, Peterson J *et al* 2000 NG2-positive oligodendrocyte progenitor cells in adult human brain and multiple sclerosis lesions. *J Neurosci* **20**: 6404–6412

Chang A, Tourtellotte WW, Rudick R, Trapp BD 2002 Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *New Engl J Med* **346**: 165–173

Chang T 1971 Recurrent viral infection (reinfection). *New Engl J Med* **284**: 765–773

Chang Y-Y, Wu H-S, Tsai T-C, Liu J-S 1994 Intractable hiccup due to multiple sclerosis: MR imaging of medullary plaque. *Can J Neurol Sci* **21**: 271–272

Chao CC, Hu S, Peterson PK 1995 Glia, cytokines, and neurotoxicity. *Crit Rev Neurobiol* **9**: 189–205

Chapenko SD, Milers A, Nora Z *et al* 2003 Correlation between HHV-6 reactivation and multiple sclerosis disease activity. *J Med Virol* **69**: 111–117

Chapman J, Sylantiev C, Nisipeanu P, Korczyn AD 1999 Preliminary observations on APOE epsilon4 allele and progression of disability in multiple sclerosis. *Arch Neurol* **56**: 1484–1487

Chapman J, Vinokurov S, Achiron A *et al* 2001 APOE is a major predictor of long term progression of disability in MS. *Neurology* **56**: 312–316

Charcot JM 1865 Sclérose du cordons lateraux del la moelle épiniere chez une femme hysterique atteinte de contracture permaneste des quatres membres. *L' Union Med* **25**: 451–457, 467–472

Charcot JM 1868a [Seance du 14 mars]. *Comptes rendus des seances et memoires lus a la societe de Biologie* **20**: 13–14

Charcot JM 1868b Histologie de la sclérose en plaques. *Gazette Hôpitaux* **41**: 554, 557–558, 566

Charcot JM 1868c Leçons sur les maladies chroniques du système nerveux. I: Des scléroses de la moelle épinière. *Gazette Hôpitaux* **41**: 405–406, 409

Charcot JM 1872 *Leçons sur les Maladies du Systeme Nerveux faites a la Salpétrière*. Paris: A. Delahaye and E. Lecrosnier, Progres Medicale, pp. 1–495 and 1–504 [*Lectures on the Diseases of the Nervous System Delivered at the Salpétrière, Sigerson G (trans.)*. London: The New Sydenham Society, 1877, pp. 157–222]

Charcot JM 1875 *Leçons sur les maladies du système nerveux faites a la Salpetrière*, 2nd edn. Paris: A. Delahaye

Charcot JM 1877 *Lectures on Diseases of the Nervous System*. London: New Sydenham Society

Charcot JM 1886 *Ouevres complètes de J.-M. Charcot. Leçons sur les maladies du système nerveux recueilles et publiées par Bourneville*. Paris: Bureau du Progres Medical and A Delahaye, Tome 1

Charcot JM 1887 *Leçons du mardi a la Salpétrière. Professeur Charcot. Polycliniques*. Paris: Bureaux du Progres Medical and A Delahaye, pp. 398–422

Chard DT, Griffin CM, Parker GJM *et al* 2002a Brain atrophy in clinically early

relapsing–remitting multiple sclerosis. *Brain* **125**: 327–337

Chard DT, Griffin CM, McLean MA *et al* 2002b Brain metabolite changes in cortical grey matter and normal appearing white matter in clinically early relapsing remitting multiple sclerosis. *Brain* **125**: 2342–2352

Chard DT, Parker GJM, Griffin CM *et al* 2002c The reproducibility and sensitivity of brain tissue volume measurements derived from an SPM-based segmentation methodology. *JMRI* **15**: 259–267

Chard DT, Brex PA, Ciccarelli O *et al* 2003 The longitudinal relation between brain lesion load and atrophy in multiple sclerosis: a 14 year follow up study. *J Neurol Neurosurg Psychiatry* **74**: 1551–1554

Chard DT, Griffin CM, Rashid W *et al* 2004 Progressive grey matter atrophy in clinically early relapsing–remitting multiple sclerosis. *Mult Scler* **10**: 387–391

Chari DM, Blakemore WF 2002a Efficient recolonisation of progenitor-depleted areas of the CNS by adult oligodendrocyte progenitor cells. *Glia* **37**: 307–313

Chari DM, Blakemore WF 2002b New insights into remyelination failure in multiple sclerosis: implications for glial cell transplantation. *Mult Scler* **8**: 271–277

Chari DM, Crang AJ, Blakemore WF 2003a Decline in rate of colonization of oligodendrocyte progenitor cell (OPC)-depleted tissue by adult OPCs with age. *J Neuropathol Exp Neurol* **62**: 908–916

Chari DM, Huang WL, Blakemore WF 2003b Dysfunctional oligodendrocyte progenitor cell (OPC) populations may inhibit repopulation of OPC depleted tissue. *J Neurosci Res* **73**: 787–793

Charles P, Hernandez MP, Stankoff B *et al* 2000 Negative regulation of central nervous system myelination by polysialylated-neural cell adhesion molecule. *Proc Natl Acad Sci USA* **97**: 7585–7590

Charles P, Reynolds R, Seilhean D *et al* 2002a Re-expression of PSA-NCAM by demyelinated axons: an inhibitor of remyelination in multiple sclerosis? *Brain* **125**: 1972–1979

Charles P, Tait S, Faivre-Sarrailh C *et al* 2002b Neurofascin is a glial receptor for the paranodin-caspr-contactin axonal complex at the axoglial junction. *Current Biol* **12**: 217–220

Charmley P, Beall SS, Concannon P *et al* 1991 Further localisation of a multiple sclerosis susceptibility gene on chromosome 7q using a new T cell receptor beta-chain DNA polymorphism. *J Neuroimmunol* **32**: 231–241

Charpentier B, Hiesse C, Lantz O *et al* 1992 Evidence that antihuman tumor necrosis factor monoclonal antibody prevents OKT3-induced acute syndrome. *Transplantation* **54**: 997–1002

Chartier-Kastler EJ, Mozer P, Denys P *et al* 2002 Neurogenic bladder management and cutaneous non-continent ileal conduit. *Spinal Cord* **40**: 443–448

Chase WMA 1959 A critique of attempts at passive transfer of sensitivity to nervous tissue. In: Kies MW, Alvord EC (eds) *Allergic Encephalomyelitis*. Springfield, IL: Thomas, pp. 348–374

Chataway SJS, Feakes R, Coraddu F *et al* 1998 The genetics of multiple sclerosis: principles, background and updated results of the United Kingdom systematic genome screen. *Brain* **121**: 1869–1887

Chataway SJS, Sawcer SJ, Coraddu F *et al* 1999a Evidence that allelic variants of the spinocerebellar ataxia type 2 gene influence susceptibility to multiple sclerosis. *Neurogenetics* **2**: 91–96

Chataway SJS, Sawcer S, Feakes R *et al* 1999b A screen of candidates from peaks of linkage: evidence for the involvement of myeloperoxidase in multiple sclerosis. *J Neuroimmunol* **98**: 208–213

Chataway SJS, Sawcer S, Sherman D *et al* 1999c No evidence for association of multiple sclerosis with the complement factors C6 and C7. *J Neuroimmunol* **99**: 150–156

Chataway SJS, Mander A, Robertson N *et al* 2001 Multiple sclerosis in sibling pairs: an analysis of 250 families. *J Neurol Neurosurg Psychiatry* **71**: 757–761

Chaudhuri A, Behan PO 2001 Acute cervical hyperextension-hyperflexion injury may precipitate and/or exacerbate symptomatic multiple sclerosis. *Eur J Neurol* **8**: 659–664

Chen C, Nagy Z, Luning Prak E, Weigert M 1995a Immunoglobulin heavy chain gene replacement: a mechanism of receptor editing. *Immunity* **3**: 747–755

Chen C, Nagy Z, Radic MZ *et al* 1995b The site and stage of anti-DNA B cell deletion. *Nature* **373**: 252–255

Chen C-H, Houchi H, Ohnaka M *et al* 1998 Nitric oxide activates Ca2+-activated K+ channels in cultured bovine adrenal chromaffin cells. *Neurosci Lett* **248**: 127–129

Chen M, Gran B, Costello K *et al* 2001 Glatiramer acetate induces a Th2-biased response and crossreactivity with myelin basic protein in patients with MS. *Mult Scler* **7**: 209–219

Chen MS, Huber AB, van der Haar ME *et al* 2000 Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1. *Nature* **403**: 434–439

Chen R, Cohen LG, Hallett M 2002 Nervous system reorganization following injury. *Neuroscience* **111**: 761–773

Chen S, Luo D, Streit WJ, Harrison JK 2002 TFG-β1 upregulates CX3CR1 expression and inhibits fractalkine-stimulated signaling in rat microglia. *J Neuroimmunol* **133**: 46–55

Chen SJ, De Vries GH 1989 The mitogenic effect of the axolemma-enriched fraction on cultured oligodendrocytes. *J Neurochem* **52**: 325

Chen W, Frank ME, Jin W, Wahl SM 2001 TGF-β released by apoptotic T cells contributes to an immunosuppressive milieu. *Immunity* **14**: 715–725

Chen Y, Devor M 1998 Ectopic mechanosensitivity in injured sensory axons arises from the site of spontaneous electrogenesis. *Eur J Pain* **2**: 165–178

Chen Y, Kuchroo VK, Inobe J *et al* 1994 Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. *Science* **265**: 1237–1240

Chen Y, Inobe J, Marks R *et al* 1995 Peripheral depletion of antigen-reactive T cells in oral tolerance. *Nature* **376**: 177–180

Chen ZJ, Ughrin Y, Levine JM 2002 Inhibition of axon growth by oligodendrocyte precursor cells. *Mol Cell Neurosci* **20**: 125–139

Cheng B, Christakos S, Mattson MP 1994 Tumor necrosis factors protect neurons against metabolic-excitotoxic insults and promote maintenance of calcium homeostasis. *Neuron* **12**: 139–153

Chevassut K 1930 The aetiology of disseminated sclerosis. *Lancet* **i**: 552–560

Chia Y-W, Fowler CF, Kamm MA *et al* 1995 Prevalence of bowel dysfunction in patients with multiple sclerosis and bladder dysfunction. *J Neurol* **242**: 105–108

Chiappa KH 1980 Pattern shift visual, brainstem auditory, and short latency somatosensory evoked potentials in multiple sclerosis. *Neurology* **30**: 110–123

Chiappa KH, Harrison JL, Brooks EB, Young RR 1980 Brainstem auditory evoked responses in 200 patients with multiple sclerosis. *Ann Neurol* **7**: 135–143

Chiara T, Carlos J, Martin D *et al* 1998 Cold effect on oxygen uptake, perceived exertion, and spasticity in patients with multiple sclerosis. *Arch Phys Med Rehab* **79**: 523–528

Chien Y-H, Jores R, Crowley MP 1996 Recognition by γ/δ T cells. *Annu Rev Immunol* **14**: 511–532

Chin RL, Latov N 2005 Peripheral neuropathy and celiac disease. *Curr Treat Options Neurol* **7**: 43–48

Ching W, Zanazzi G, Levinson SR, Salzer JL 1999 Clustering of neuronal sodium channels requires contact with myelinating Schwann cells. *J Neurocytol* **28**: 295–301

Chiocchetti A, Comi C, Indelicato M *et al* 2005 Osteopontin gene haplotypes correlate with multiple sclerosis development and progression. *J Neuroimmunol* **163**: 172–178

Chitnis T, Najafian N, Abdallah KA *et al* 2001 CD28-independent induction of experimental autoimmune encephalomyelitis. *J Clin Invest* **107**: 575–583

Chiu SY, Ritchie JM 1980 Potassium channels in nodal and internodal axonal membrane of mammalian myelinated fibres. *Nature* **284**: 170–171

Chiu SY, Ritchie JM 1981 Evidence for the presence of potassium channels in the paranodal region of acutely demyelinated mammalian single nerve fibres. *J Physiol* **313**: 415–437

Chluba J, Steeg C, Becker A *et al* 1989 T cell receptor β chain usage in myelin basic protein-specific rat T lymphocytes. *Eur J Immunol* **19**: 279–284

Chmielewska-Badora J, Cisak E, Dutkiewicz J 2000 Lyme borreliosis and multiple sclerosis: any connection? A seroepidemic study. *Ann Agric Environ Med* **7**: 141–143

Chofflon M, Juillard C, Juillard P, Gauthier G, Grau GE 1992 Tumor necrosis factor α production as a possible predictor of relapse in patients with multiple sclerosis. *Eur Cytokine Netw* **3**: 523–531

Choi YB, Lipton SA 2000 Redox modulation of the NMDA receptor. *Cell Mol Life Sci* **57**: 1535–1541

Chong HT, Li PCK, Ong B *et al* 2002 Severe spinal cord involvement is a universal feature of Asians with multiple sclerosis: a joint Asian study. *Neurol J Southeast Asia* **7**: 35–40

Chopra JS, Radhakrishnan K, Sawhney BB *et al* 1980 Multiple sclerosis in north-west India. *Acta Neurol Scand* **62**: 312–321

Chou YK, Buenafe AC, Dedrick R *et al* 1994 T cell receptor Vβ gene usage in the recognition of myelin basic protein by cerebrospinal fluid- and blood-derived T cells from patients with multiple sclerosis. *J Neurosci Res* **37**: 169–181

Christensen T, Sorensen PD, Hansen HJ, Moller-Larsen A 2003 Antibodies against a human endogenous retrovirus and the preponderance of env splice variants in multiple sclerosis patients. *Mult Scler* **9**: 6–15

Christopher V, Scolding N, Przemioslo RT 2005 Acute hepatitis secondary to interferon beta-1a in multiple sclerosis. *J Neurol* **252**: 855–856

Chrousos GA, Kattah JC, Beck RW, Cleary PA, the Optic Neuritis Study Group 1993 Side effects of glucocorticoid treatment. Experience of the Optic Neuritis Treatment Trial. *J Am Med Assoc* **269**: 2110–2112

Chu CQ, Wittmer S, Dalton DK 2000 Failure to suppress the expansion of the activated CD4 T cell population in interferon gamma-deficient mice leads to exacerbation of experimental autoimmune encephalomyelitis. *J Exp Med* **192**: 123–128

Chun SJ, Rasband MN, Sidman RL *et al* 2003 Integrin-linked kinase is required for laminin-2-induced oligodendrocyte cell spreading and CNS myelination. *J Cell Biol* **163**: 397–408

Cianchetti C, Zuddas A, Randazzo AP *et al* 1999 Lamotrigine adjunctive therapy in painful phenomena in MS: preliminary observations. *Neurology* **53**: 433

Ciccarelli O, Werring DJ, Wheeler-Kingshott CA *et al* 2001 Investigation of MS normal-appearing brain using diffusion tensor MRI with clinical correlations. *Neurology* **56**: 926–933

Ciccarelli O, Parker GJM, Toosy AT *et al* 2003a From diffusion tractography to quantitative white matter tract measures: a reproducibility study. *NeuroImage* **18**: 348–359

Ciccarelli O, Toosy AT, Parker GJM *et al* 2003b Diffusion tractography based group mapping of major white-matter pathways in the human brain. *Neuroimage* **19**: 1545–1555

Ciccarelli O, Toosy AT, Hickman SJ *et al* 2005 Optic radiation changes after optic neuritis detected by tractography-based group mapping. *Hum Brain Mapping* **25:** 308–316

Cid C, Alcazar A, Regidor I *et al* 2002 Neuronal apoptosis induced by cerebrospinal fluid from multiple sclerosis patients correlates with hypointense lesions on T1 magnetic resonance imaging. *J Neurol Sci* **193**: 103–109

Cid C, Alvarez-Cermeno JC, Regidor I *et al* 2003 Caspase inhibitors protect against neuronal apoptosis induced by cerebrospinal fluid from multiple sclerosis patients. *J Neuroimmunol* **136**: 119–124

Cifelli A, Matthews PM 2002 Cerebral plasticity in multiple sclerosis. *Mult Scler* **8**: 193–199

Cifelli A, Arridge M, Jezzard P *et al* 2002 Thalamic neurodegeneration in multiple sclerosis. *Ann Neurol* **52**: 650–653

Ciric B, Howe CL, Paz Soldan M *et al* 2003 Human monoclonal IgM antibody promotes CNS myelin repair independent of Fc function. *Brain Pathol* **13**: 608–616

Ciric B, Van Keulen V, Paz Soldan M *et al* 2004 Antibody-mediated remyelination operates through mechanism independent of immunomodulation. *J Neuroimmunol* **146**: 153–161

Ciusani E, Allen M, Sandberg-Wollheim M *et al* 1995 Analysis of HLA-class II DQA1, DQB1, DRB1 and DPB1 in Italian multiple sclerosis patients. *Eur J Immunogenet* **22**: 171–178

Ciusani E, Gelati M, Frigerio S *et al* 2001 Modulation of experimental allergic encephalomyelitis in Lewis rats by administration of a peptide of Fas ligand. *J Autoimmun* **17**: 273–280

Clanet M, Radue EW, Kappos L *et al* 2002 A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS. *Neurology* **59**: 1507–1517

Clanet M, Kappos L, Hartung HP *et al* 2004 Interferon beta-1a in relapsing multiple sclerosis: four-year extension of the European IFNbeta-1a Dose-Comparison Study. *Mult Scler* **10**: 139–144

Clark AJ, Ware MA, Yazer E *et al* 2004 Patterns of cannabis use among patients with multiple sclerosis. *Neurology* **62**: 2098–2100

Clark EA, Lane PJL 1991 Regulation of human B cell activation and adhesion. *Ann Rev Immunol* **9**: 97–128

Clark RB, Lingenheld EG 1998 Adoptively transferred EAE in γδ T cell knock-out mice. *J Autoimmun* **11**: 105–110

Clark VA, Detels R, Visscher BR *et al* 1982 Factors associated with a malignant or benign course of multiple sclerosis. *J Am Med Assoc* **248**: 856–860

Clear D 1999 Anaphylactoid reaction to methyl prednisolone developing after starting treatment with interferon beta-1b. *J Neurol Neurosurg Psychiatry* **66**: 690

Clegg A, Bryant J 2001 Immunomodulatory drugs for multiple sclerosis: a systematic review of clinical and cost effectiveness. *Expert Opin Pharmacother* **2**: 623–639

Clemen CS, Spottke EA, Lütjohann D *et al* 2005 Cerebrotendinous xanthomatosis: at treatable ataxia. *Neurology* **64**: 1476

Clements JM, Cossins JA, Wells GM *et al* 1997 Matrix metalloproteinase expression during experimental autoimmune encephalomyelitis and effects of a combined matrix metalloproteinase and tumour necrosis factor-alpha inhibitor. *J Neuroimmunol* **74**: 85–94

Clerget-Darpoux F, Govaerts A, Feingold N 1984 HLA and susceptibility to multiple sclerosis. *Tissue Antigens* **24**: 160–169

Clerici M, Fernandez M 1992 Restriction fragment length polymorphism analysis of HLA-DR and DQ-linked alleles in multiple sclerosis in Spain. *J Neuroimmunol* **41**: 245–248

Clerici M, Shearer GM 1993 A Th1 to Th2 switch is a critical step in the etiology of HIV infection. *Immunol Today* **14**: 107–111

Clerici M, Fusi ML, Caputo D *et al* 1999 Immune responses to antigens of human endogenous retroviruses in patients with acute or stable multiple sclerosis. *J Neuroimmunol* **99**: 173–182

Clifford DB 1983 Tetrahydro-cannabinol for treatment of multiple sclerosis. *Ann Neurol* **13**: 669–671

Clifford DB, Trotter JL 1984 Pain in multiple sclerosis. *Arch Neurol* **41**: 1270–1272

Clifford-Jones RE, Cunningham K, Halliday AM *et al* 1985a Visual evoked potentials in meningiomas compressing the anterior visual pathways. *Electroencephalography and Clin Neurophysiol* **61**: S52

Clifford-Jones RE, McDonald WI, Landon DN 1985b Chronic optic nerve compression: an experimental study. *Brain* **108**: 241–262

Cocco E, Mancosu C, Fadda E *et al* 2002 Lack of evidence for a role of the myelin basic protein gene in multiple sclerosis susceptibility in Sardinian patients. *J Neurol* **249**: 1552–1555

Cocco E, Sardu C, Lai M *et al* 2004a Anticipation of age at onset in multiple sclerosis: a Sardinian cohort study. *Neurology* **62**: 1794–1798

Cocco E, Murru MR, Melis C *et al* 2004b PTPRC (CD45) C77G mutation contribution to multiple sclerosis susceptibility in Sardinian patients. *J Neurol* **251**: 1085–1088

Cock H, Mandler R, Ahmed W, Schapira AHV 1997 Neuromyelitis optica (Devic's syndrome): no association with the primary mitochondrial DNA mutations found in Leber hereditary optic neuropathy. *J Neurol Neurosurg Psychiatry* **62**: 85–87

Coffey RJ, Cahill D, Steers W *et al* 1993 Intrathecal baclofen for intractable spasticity of spinal origin: results of a long term multicenter study. *J Neurosurg* **78**: 226–232

Coffman RL, von der Weid T 1997 Multiple pathways for the initiation of T helper 2 (Th2) responses. *J Exp Med* **185**: 373–375

Cogan MS, Kline LB, Duvall ER 1987 Bilateral internuclear ophthalmoplegia in systemic lupus erythematosus. *J Clin Neuroophthalmol* **7**: 69–73

Cogle CR, Yachnis AT, Laywell ED *et al* 2004 Bone marrow transdifferentiation in brain after transplantation: a retrospective study. *Lancet* **363**: 1432–1437

Cohen D, Cohen O, Marcadet A *et al* 1984 Class II HLA-DC beta-chain DNA restriction fragments differentiate among HLA-DR2 individuals in insulin-dependent diabetes and multiple sclerosis. *Proc Natl Acad Sci USA* **81**: 1774–1778

Cohen IR 1992 The cognitive paradigm and the immunological homunculus. *Immunol Today* **13**: 490–494

Cohen IR, Miller A (eds) 1994 *Autoimmune Disease Models: A Guidebook*. New York: Academic Press

Cohen IR, Young DB 1991 Autoimmunity, microbial immunity and the immunological homunculus. *Immunol Today* **12**: 105–110

Cohen JA, Cutter GR, Fischer JS *et al* 2002 Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. *Neurology* **59**: 679–687

Cohen L 1965 Disturbance of taste as a symptom of multiple sclerosis. *Br J Oral Surg* **2**: 184–185

Cohen L, Macrae D 1962 Tumors in the region of the foramen magnum. *J Neurosurg* **19**: 462–469

Cohen MM, Lessell S, Wolf PA 1979 A prospective study of the risk of developing multiple sclerosis in uncomplicated optic neuritis. *Neurology* **29**: 208–213

Cohen O, Biran I, Steiner I 2000 Cerebrospinal fluid oligoclonal IgG bands in patients with spinal arteriovenous malformation and structural central nervous system lesions. *Arch Neurol* **57**: 553–557

Cohen O, Steiner-Birmanns B, Biran I *et al* 2001 Recurrence of acute disseminated encephalomyelitis at the previously affected brain site. *Arch Neurol* **58**: 797–801

Cohen RA, Fisher M 1989 Amantidine treatment of fatigue associated with multiple sclerosis. *Arch Neurol* **46**: 676–680

Cohen SR, Brune MJ, Herndon RM, McKhann GM 1978 Cerebrospinal fluid myelin basic protein and multiple sclerosis. *Adv Exp Med Biol* **100**: 513–519

Cole GF, Auchterlonie LA, Best PV 1995 Very early onset multiple sclerosis. *Dev Med Child Neurol* **37**: 667–672

Colello RJ, Pott U, Schwab ME 1994 The role of oligodendrocytes and myelin on axon maturation in the developing rat retinofugal pathway. *J Neurosci* **14**: 2594–2605

Colello RJ, Devey RL, Imperato E, Pott U 1995 The chronology of oligodendrocyte differentiation in the rat optic nerve: evidence for a signalling step initiating myelination in the CNS. *J Neurosci* **15**: 7665–7672

Coleman RJ, Quinn NP, Marsden CD 1988 Multiple sclerosis presenting as adult onset dystonia. *Mov Disord* **3**: 329–332

Coles AJ, Paolili A, Molyneux P *et al* 1999a Monoclonal antibody treatment exposes three mechanisms underlying the clinical course in multiple sclerosis. *Ann Neurol* **46**: 296–304

Coles AJ, Wing M, Smith S *et al* 1999b Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. *Lancet* **354**: 1691–1695

Coles AJ, Le Page E, Cox AL *et al* 2005 The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy in relapsing–remitting and secondary progressive disease. *J Neurol* [epub ahead of print]

Collard RC, Koehler RPM, Mattson DH 1997 Frequency and significance of antinuclear antibodies in multiple sclerosis. *Neurology* **49**: 857–861

Collins M, Goodfellow P, Spurr N *et al* 1985 The human T cell receptor alpha chain gene maps to chromosome 14. *Nature* **314**: 273–274

Colognato H, Baron W, Avellana-Adalid V *et al* 2002 CNS integrins switch growth factor signalling to promote target-dependent survival. *Nat Cell Biol* **4**: 833–841

Colombo B, Boneschi FM, Rossi P *et al* 2000 MRI and motor evoked potential findings in nondisabled multiple sclerosis patients with and without symptoms of fatigue. *J Neurol* **247**: 506–509

Colosimo C, Pozzilli C, Frontoni M *et al* 1997 No increase of serum autoantibodies during therapy with recombinant human interferon-beta1a in relapsing-remitting multiple sclerosis. *Acta Neurol Scand* **96:** 372–374

Columba-Cabezas S, Serafini B, Ambrosini E, Aloisi F 2003 Lymphoid chemokines CCL19 and CCL21 are expressed in the central nervous system during experimental autoimmune encephalomyelitis: implications for the maintenance of chronic neuroinflammation. *Brain Pathol* **13**: 38–51

Comabella M, Altet L, Peris F *et al* 2004 Genetic analysis of SLCI IAI polymorphisms in multiple sclerosis patients. *Mult Scler* **10**: 618–620

Comi G, Hartung H 2005 Evidence for use of glatiramer acetate in multiple sclerosis.[comment]. *Lancet Neurol* **4**: 75–76; discussion 76–77

Comi G, Martinelli V, Giuliani G *et al* 1989 Incidence of multiple sclerosis in Italy: a multicenter study. In: Bataglia MA (ed.) *Multiple Sclerosis Research*. Amsterdam: Elsevier, pp. 159–163

Comi G, Filippi M, Martenelli V *et al* 1995 Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. *J Neurol Sci* **132**: 222–227

Comi G, Rovaris M, Falautano M *et al* 1999 A multiparametric MRI study of frontal lobe dementia in multiple sclerosis. *J Neurol Sci* **171**:135–144

Comi G, Kappos L, Clanet M *et al* 2000 Guidelines for autologous blood and marrow stem cell transplantation in multiple sclerosis: a consensus report written on behalf of the European Group for Blood and Marrow Transplantation and the European Charcot Foundation. BMT-MS Study Group. *J Neurol* **247**: 376–382

Comi G, Filippi M, Barkhof F *et al* 2001a Effect of early interferon treatment on conversion to definite multiple sclerosis. *Lancet* **357**: 1576–1582

Comi G, Filippi M, Wolinsky JS 2001b European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. *Ann Neurol* **49**: 290–297

Comi G, Leocani L, Colombo B, Rossi P 2002 Pathophysiology and treatment of fatigue in multiple sclerosis. In: Abramsky O, Compston DAS, Miller A, Said G (eds) *Brain Disease – Therapeutic Strategies and Repair*. London: Martin Dunitz, pp. 389–394

Compston DAS 1981 Multiple sclerosis in the Orkneys. *Lancet* **ii**: 98

Compston DAS 1988 The 150th anniversary of the first depiction of the lesions of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **51**: 1249–1252

Compston DAS 1990a The dissemination of multiple sclerosis. *J R Coll Physicians Lond* **24**: 207–218

Compston DAS 1990b Risk factors for multiple sclerosis: race or place? *J Neurol Neurosurg Psychiatry* **53**: 821–823

Compston DAS 1995 Brain repair. *J Intern Med* **237**: 127–134

Compston DAS 1997 Remyelination in multiple sclerosis: a challenge for therapy. The Charcot Lecture for 1996: European Charcot Foundation. *Mult Scler* **3**: 51–70

Compston DAS 2003 Revisiting The pathogenesis of multiple sclerosis revisited. *The International MS Journal* **10**: 29–31

Compston DAS 2004 The marvellous harmony of the nervous parts: the origins of multiple sclerosis. *Clin Med* **4**: 346–354

Compston DAS, Coles AJ 2002 Multiple sclerosis. *Lancet* **359**: 1221–1231

Compston DAS, Howard S 1982 HLA typing in multiple sclerosis. *Lancet* **ii**: 661

Compston DAS, Swingler RJ 1989 Life expectancy in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **52**: 1312

Compston DAS, Batchelor JR, McDonald WI 1976 B lymphocyte alloantigens associated with multiple sclerosis. *Lancet* **ii**: 1261–1265

Compston DAS, Batchelor JR, Earl CJ, McDonald WI 1978 Factors influencing the risk of multiple sclerosis in patients with optic neuritis. *Brain* **101**: 495–512

Compston DAS, Vakarelis BN, Paul E *et al* 1986 Viral infection in patients with multiple sclerosis and HLA-DR matched controls. *Brain* **109**: 325–344

Compston DAS, Hughes PJ, Morgan BP, Gibbs J, Milligan NM 1987 High dose

methylprednisolone in the treatment of multiple sclerosis. 2. Immunological effects. *J Neurol Neurosurg Psychiatry* **50**: 517–522
Compston DAS, Morgan BP, Campbell AK *et al* 1989 Immunocytochemical localisation of the terminal complement complex in multiple sclerosis. *Neuropathol Appl Neurobiol* **15**: 307–316
Compston ND 1953 Disseminated sclerosis: assessment of the effect of treatment on the course of the disease. *Lancet* **ii**: 271–275
de la Concha EG, Arroyo R, Crusius JBA *et al* 1997 Combined effect of HLA-DRB1*1501 and interleukin-1 receptor antagonist gene allele 2 in susceptibility to relapsing/remitting multiple sclerosis. *J Neuroimmunol* **80**: 172–178
Confavreux C 1977 *L'histoire naturelle de la sclérose en plaques. Etude par informatique de 349 observations.* Thèse de Médecine, Université Claude Bernard, Lyon 184 pp.
Confavreux C 1994 Establishment and use of multiple sclerosis registers – EDMUS. *Ann Neurol* **36 (Suppl)**: 136–139
Confavreux C 2002 Relapses, progression, inflammation and neurodegeneration in multiple sclerosis: a changing view. *Adv Clin Neurosci Rehab* **2**: 7–9
Confavreux C, Paty DW 1995 Current status of computerization of multiple sclerosis clinical data for research in Europe and North America: the EDMUS / MS – COSTAR connection. *Neurology* **45**: 573–576
Confavreux C, Vukusic S 2002 Natural history of multiple sclerosis: implications for counselling and therapy. *Curr Opin Neurol* **15**: 257–266
Confavreux C, Vukusic S 2004 Non-specific immunosuppressants in the treatment of multiple sclerosis. *Clin Neurol Neurosurg* **106**: 263–269
Confavreux C, Vukusic S 2005a Age at disability milestones in multiple sclerosis (submitted)
Confavreux C, Vukusic S 2005b Natural course of multiple sclerosis: a unifying concept (submitted)
Confavreux C, Wolfson C 1989 Mathematical models and individualized outcome estimates in multiple sclerosis. *Biomed Pharmacother* **43**: 675–680
Confavreux C, Aimard D, Devic M 1980 Course and prognosis of multiple sclerosis assessed by the computerised data processing of 349 patients. *Brain* **103**: 281–300
Confavreux C, Chapuis-Cellier C, Arnaud P *et al* 1986 Oligoclonal 'fingerprint' of CSF IgG in multiple sclerosis patients is not modified following intrathecal administration of natural beta-interferon. *J Neurol Neurosurg Psychiatry* **49**: 1308–1312
Confavreux C, Darchy P, Alperovitch A *et al* 1987 Le Sud-Est francais, zone à haut risque de sclérose en plaques? *Presse Medicale* **16**: 622–623
Confavreux C, Compston DAS, Hommes OR *et al* 1992 EDMUS, an European database for multiple sclerosis. *J Neurol Neurosurg Psychiatry* **55**: 671–676
Confavreux C, Moreau T, Jouvet A *et al* 1993 Association sclérose latérale amyotrophique et sclérose en plaques. *Rev Neurol* **149**: 351–353
Confavreux C, Hours M, Moreau T *et al* 1996 Clinical databasing in multiple sclerosis: EDMUS and the European effort. In: Abramsky O (ed.) *Frontiers in Multiple Sclerosis: Clinical Research and Therapy.* London: Martin Dunitz, pp. 299–312
Confavreux C, Grimaud J, Vukusic S, Moreau T 1998a Peut-on prédire l'évolution de la sclérose en plaques? *Rev Neurol* **154**: 624–628
Confavreux C, Hutchinson M, Hours M *et al* 1998b Rate of pregnancy-related relapse in multiple sclerosis. *N Engl J Med* **339**: 285–291
Confavreux C, Vukusic S, Moreau T, Adeleine P 2000 Relapses and progression of disability in multiple sclerosis. *N Engl J Med* **343**: 1430–1438
Confavreux C, Suissa S, Saddier P *et al* 2001 Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group. *New Engl J Med* **344**: 319–326
Confavreux C, Vukusic S, Adeleine P 2003 Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* **126**: 770–782
Conférence de Consensus sur la sclérose en plaques. Paris, 7 et 8 juin 2001 Recommandations du jury. *Rev Neurol* **157**: 1184–1192
Consroe P, Musty R, Rein J *et al* 1997 The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* **38**: 44–48
Constant SL, Bottomly K 1997 Induction of the Th1 and Th2 $CD4^+$ T cell response: alternative approaches. *Annu Rev Immunol* **15**: 297–322
Constantinescu CS, Raps EC, Cohen JA *et al* 1994 Olfactory disturbances as the initial or most prominent symptom of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **57**: 1011–1012
Constantinescu CS, Whiteley A, Blumhardt LD 2000 Long term azathioprine fails to prevent onset of multiple sclerosis: report of two cases. *Mult Scler* **6**: 362–363
Contini C, Cultrera R, Seraceni S *et al* 2004 Cerebrospinal fluid molecular demonstration of *Chlamydia pneumoniae* DNA is associated to clinical and brain magnetic resonance imaging activity in a subset of patients with relapsing–remitting multiple sclerosis. *Mult Scler* **10**: 360–369
Cook JH, Arden GB 1977 Unilateral retrobulbar neuritis: a comparison of evoked potentials and psychophysical measurements. In: Desmedt JE (ed.) *Visual Evoked Potentials in Man: New Development*. Oxford, Clarendon Press, pp. 450–457
Cook SD 2000 Trauma does not precipitate multiple sclerosis. *Arch Neurol* **57**: 1077–1078
Cook SD, Dowling PC 1982 MS in Iceland revisited. *Neurology* 32: 1204–1205
Cook SD, Dowling PC, Russell WC 1978 Multiple sclerosis and canine distemper. *Lancet* **i**: 605–606
Cook SD, Gudmundsson G, Benedikz J, Dowling PC 1980 Multiple sclerosis and distemper in Iceland, 1966–1978. *Acta Neurol Scand* **61**: 244–251
Cook SD, Cromarty MB, Tapp W *et al* 1985 Declining incidence of multiple sclerosis in the Orkney Islands. *Neurology* **35**: 545–551
Cook SD, Devereux C, Triano R *et al* 1986 Effect of total lymphoid irradiation in chronic progressive multiple sclerosis. *Lancet* **i**: 1405–1409
Cook SD, Blumberg B, Dowling PC *et al* 1987 Multiple sclerosis and canine distemper on Key West, Florida. *Lancet* **i**: 1426–1427
Cook SD, MacDonald J, Tapp W *et al* 1988 Multiple sclerosis in the Shetland Islands: an update. *Acta Neurol Scand* **77**: 148–151
Cook SD, Triano R, Rohowsky-Kochan C *et al* 1992 Gamma globulin in progressive multiple sclerosis. *Acta Neurol Scand* **86**: 171–175
Cook SD, Devereux C, Triano R *et al* 1995 Combination total lymphoid irradiation and low dose corticosteroid therapy for progressive multiple sclerosis. *Acta Neurol Scand* **91**: 22–27
Cooke RG 1990 MS in the Faroe Islands and the possible protective effect of ealy childhood exposure to the 'MS agent'. *Acta Neurol Scand* **82**: 230–233
Cooke WT, Smith WT 1966 Neurological disorders associated with adult celiac disease. *Brain* **89**: 683–722
Cooney BS, Grossman RI, Farber RE 1996 Frequency of magnetic resonance abnormalities in patients with migraine. *Headache* **36**: 616–621
Copolymer 1 Multiple Sclerosis Study Group. *Neurology* **50**: 701–708
Coppin H, Ribouchon M-T, Bausero P *et al* 2000 No evidence for transmission disequilibrium between a new marker at the myelin basic protein locus and multiple sclerosis in French patients. *Genes Immun* **1**: 478–482
Coraddu F, Reyes-Yanez MP, Aladro Y *et al* 1998a HLA associations with multiple sclerosis in the Canary Islands. *J Neuroimmunol* **87**: 130–135
Coraddu F, Sawcer S, Feakes R *et al* 1998b HLA typing in the United Kingdom multiple sclerosis genome screen. *Neurogenetics* **2**: 24–33
Coraddu F, Sawcer S, D'Alfonso S *et al* 2001 A genome screen for multiple sclerosis in Sardinian multiplex families. *Eur J Hum Gen* **9**: 621–626
Coraddu F, Lai M, Mancosu C *et al* 2003 A genome-wide screen for linkage disequilibrium in Sardinian multiple sclerosis. *J Neuroimmunol* **143**: 120–123
Cordier AC, Haumont SM 1980 Development of thymus, parathyroids, and ultra-branchial bodies in NMRI and nude mice. *Am J Anat* **157**: 227–263

Cordonnier C, De Sèze J, Breteau G *et al* 2003 Prospective study of patients presenting with acute partial transverse myelopathy. *J Neurol* **250**: 1447–1452

Corley SM, Ladiwala U, Besson A, Yong VW 2001 Astrocytes attenuate oligodendrocyte death in vitro through an alpha(6) integrin-laminin-dependent mechanism. *Glia* **36**: 281–294

Cornblath WT, Quint DJ 1997 MRI in optic nerve enlargement in optic neuritis. *Neurology* **48**: 821–825

Corona T, Leon C, Ostrosky-Zeichner L 1999 Severe anaphylaxis with recombinant interferon beta. *Neurology* **52**: 425

Correale J, Gilmore W, McMillan M *et al* 1995a Patterns of cytokine secretion by autoreactive proteolipid protein-specific T cell clones during the course of multiple sclerosis. *J Immunol* **154**: 2959–2968

Correale J, McMillan M, Le T, Weiner LP 1995b Isolation and characterization of autoreactive proteolipid protein peptide specific T cell clones from multiple sclerosis patients. *Neurology* **45**: 1370–1378

Corrette BJ, Repp H, Dreyer F, Schwarz JR 1991 Two types of fast K+ channels in rat myelinated nerve fibres and their sensitivity to dendrotoxin. *Pflugers Arch Eur J Physiol* **418**: 408–416

Corsini E, Gelati M, Dufour A et al 1997 Effects of β-interferon-1b treatment in MS patients on adhesion between PBMNCs, HUVECs and MS-HBECs: an *in vivo* and *in vitro* study. *J Neuroimmunol* **79**: 76–83

Cortese I, Tafi R, Grimaldi LME *et al* 1996 Identification of peptides specific for cerebrospinal fluid antibodies in multiple sclerosis by using phage libraries. *Proc Natl Acad Sci USA* **93**: 11063–11067

Cortese I, Capone S, Luchetti S *et al* 1998 CSF-enriched antibodies do not share specificities among MS patients. *Mult Scler* **4**: 118–123

Cortese I, Capone S, Luchetti S *et al* 2001 Cross-reactive phage-displayed mimotopes lead to the discovery of mimicry between HSV-1 and a brain-specific protein. *J Neuroimmunol* **113**: 119–128

Cosby SL, McQuaid S, Taylor MJ *et al* 1989 Examination of eight cases of multiple sclerosis and 56 neurological and non-neurological controls for genomic sequences of measles virus, canine distemper virus, simian virus 5 and rubella virus. *J Gen Virol* **70**: 2027–2036

Cosnett JE 1973 Neurological disease in Natal. In: JD Spillane (ed.) *Tropical Neurology*. London: Oxford University Press, pp. 259–272

Cosnett JE 1981a Multiple sclerosis and neuromyelitis optica. Case report and speculation. *S Afr Med J* **60**: 249–251

Cosnett JE 1981b Multiple sclerosis and neuromyelitis optica in tropical and subtropical countries. *Med Hypotheses* **7**: 61–63

Cossins JA, Clements JM, Ford J *et al* 1997 Enhanced expression of MMP-7 and MMP-9 in demyelinating multiple sclerosis lesions. *Acta Neuropathol* **94**: 590–598

Costa JL, Diazgranados JA 1994 Ivermectin for spasticity in spinal cord injury. *Lancet* **343**: 739

Cotton F, Weiner HL, Jolesz FA *et al* 2003 MRI contrast uptake in new lesions in relapsing–remitting MS followed at weekly intervals. *Neurology* **60**: 640–646

Cottrell DA, Kremenchutzky M, Rice GPA *et al* 1999a The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. *Brain* **122**: 625–639

Cottrell DA, Kremenchutzky M, Rice GPA *et al* 1999b The natural history of multiple sclerosis: a geographically based study. 6. Applications to planning and interpretation of clinical therapeutic trials in primary progressive multiple sclerosis. *Brain* **122**: 641–647

Cottrell SS, Wilson SAK 1926 The affective symptomatology of disseminated sclerosis. *J Neurol Psychopathol* **7**: 1–50

Cournu-Rebeix I, Genin E, Lesca G *et al* 2003 Intercellular adhesion molecule-1: a protective haplotype against multiple sclerosis. *Genes Immun* **4**: 518–523

Courville CB 1968 Acute lesions of multiple sclerosis – possible significance of vascular changes. *J Neuropathol Exp Neurol* **27**: 159 (abstract)

Courville CB 1970 Concentric sclerosis. In: Vinken PJ, Bruyn GW (eds) *Handbook of Clinical Neurology*. Amsterdam: Elsevier, Vol 9, pp. 437–451

Coustans M, Leray E, Le Page E *et al* 2004 Both relapsing–remitting and primary progressive multiple sclerosis are a two-stage disease, suggesting two consecutive mechanisms underlying the progression of disability in multiple sclerosis. *Mult Scler* **10 (Suppl)**: S111

Cowan EP, Pierce ML, MacFarland HF, McFarlin DE 1991a HLA-DR and DQ allelic sequences in multiple sclerosis patients are identical to those found in the general population. *Hum Immunol* **32**: 203–210

Cowan EP, Pierce M, Dhib-Jalbut S 1991b Interleukin-1 downregulates HLA class I expression on a human glioblastoma cell line. *J Neuroimmunol* **33**: 17–28

Cowan J, Ormerod IEC, Rudge P 1990 Hemiparetic multiple sclerosis. *J Neurol Neurosurg Psychiatry* **53**: 675–680

Cowan JM, Dick JPR, Day BL, Rothwell JC, Thompson PD, Marsden CD 1984 Abnormalities in central motor pathway conduction in multiple sclerosis. *Lancet* **ii**: 304–307

Coward DM 1994 Tizanidine: neuropharmacology and mechanism of action. *Neurology* **44 (Suppl 9)**: S6–S11

Cox AL, Coles AJ, Antoun N *et al* 2005 Recurrent myelitis and optic neuritis in a 29-year-old woman. *Lancet Neurol* **4**: 510–516

Cox DR 1972 Regression models and life tables. *J R Stat Soc Series B* **34**: 187–220

Coyle PK 1989 Borrelia burgdorferi antibodies in multiple sclerosis patients. *Neurology* **39**: 760–761

Coyle PK 2002 Lyme disease. *Cur Neurol Neurosci Rep* **2**: 479–487

Coyle PK, Krupp LB, Doscher C 1993 Significance of reactive Lyme serology in multiple sclerosis. *Ann Neurol* **34**: 745–747

Craelius W, Migdal MW, Luessenhop CP *et al* 1982 Iron deposits surrounding multiple sclerosis plaques. *Arch Pathol Lab Med* **106**: 397–399

Craig J, Young CA, Ennis M *et al* 2003 A randomised controlled trial comparing rehabilitation against standard therapy in multiple sclerosis patients receiving intravenous steroid treatment. *J Neurol Neurosurg Psychiatry* **74**: 1225–1230

Craner MJ, Zajicek JP 2001 Immunosuppressive treatments in MS – side effects from azathioprine. *J Neurol* **248**: 625–626

Craner MJ, Lo AC, Black JA *et al* 2003a Annexin II/p11 is up-regulated in Purkinje cells in EAE and MS. *NeuroReport* **14**: 555–558

Craner MJ, Lo AC, Black JA, Waxman SG 2003b Abnormal sodium channel distribution in optic nerve axons in a model of inflammatory demyelination. *Brain* **126**: 1552–1561

Craner MJ, Hains BC, Lo AC *et al* 2004a Co-localization of sodium channel Nav1.6 and the sodium-calcium exchanger at sites of axonal injury in the spinal cord in EAE. *Brain* **127**: 294–303

Craner MJ, Newcombe J, Black JA *et al* 2004b Molecular changes in neurons in multiple sclerosis: altered axonal expression of Nav1.2 and Nav1.6 sodium channels and Na+/Ca2+ exchanger. *Proc Natl Acad Sci USA* **101**: 8168–8173

Craner MJ, Damarjian TG, Liu S *et al* 2005 Sodium channels contribute to microglia/macrophage activation in EAE and MS. *Glia* **49**: 220–229

Crang AJ, Gilson J, Blakemore WF 1998 The demonstration by transplantation of the very restricted remyelinating potential of post-mitotic oligodendrocytes. *J Neurocytol* **27**: 541–553

Crang AJ, Gilson JM, Li WW, Blakemore WF 2004 The remyelinating potential and in vitro differentiation of MOG-expressing oligodendrocyte precursors isolated from the adult rat CNS. *Eur J Neurosci* **20**: 1445–1460

Craven RA, Totty N, Harnden P *et al* 2002 Laser capture microdissection and two-dimensional polyacrylamide gel electrophoresis: evaluation of tissue preparation and sample limitations. *Am J Pathol* **160**: 815–822

Crawley F, Saddeh I, Barker S, Katifi H 2001 Acute pulmonary oedema: presenting symptoms of multiple sclerosis. *Mult Scler* **7**: 71–72

Crecelius W 1928 Uber Antimonbehandlung der multiplen Sklerose. *Deutsche Medizinische Wochenschrift* **54**: 1332–1334

Cree BAC, Goodin DS, Hauser SL 2002 Neuromyelitis optica. *Semin Neurol* **22**: 105–122

Cree BAC, Khan O, Bourdette D *et al* 2004 Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. *Neurology* **63**: 2039–2045

Cree BA, Lamb S, Morgan K *et al* 2005 An open label study of the effects of rituximab in neuromyelitis optica. *Neurology* **64**: 1270–1272

Cripps J, Rudd A, Ebers GC 1982 Birth order and multiple sclerosis. *Acta Neurol Scand* **66**: 342–346

Critchley M 1969 Four illustrious neuroluetics. *Proc R Soc Med* **62**: 669–673

Crockard AD, Treacy MT, Droogan AG *et al* 1995 Transient immunomodulation by intravenous methylprednisolone treatment of multiple sclerosis. *Mult Scler* **1**: 20–24

Crockard AD, Treacy MT, Droogan AG, Hawkins SA 1996 Methylprednisolone attenuates interferon-beta induced expression of HLA-DR on monocytes. *J Neuroimmunol* **70**: 29–35

Cross AH, Cannella B, Brosnan CF, Raine CS 1990 Homing to central nervous system vasculature by antigen-specific lymphocytes. I. Localization of ^{14}C-labelled cells during acute, chronic, and relapsing experimental allergic encephalomyelitis. *Lab Invest* **63**: 162–170

Cross AH, Cannella B, Brosnan CF, Raine CS 1991 Hypothesis: antigen-specific T cells prime central nervous system endothelium for recruitment of nonspecific inflammatory cells to effect autoimmune demyelination. *J Neuroimmunol* **33**: 237–244

Cross AH, Tuohy VK, Raine CS 1993 Development of reactivity to new myelin antigens during chronic relapsing autoimmune demyelination. *Cell Immunol* **146**: 261–269

Cross AH, Manning PT, Keeling RM *et al* 1998 Peroxynitrite formation within the central nervous system in active multiple sclerosis. *J Neuroimmunol* **88**: 45–56

Cross AH, San M, Stern MK *et al* 2000 A catalyst of peroxynitrite decomposition inhibits murine experimental autoimmune encephalomyelitis. *J Neuroimmunol* **107**: 21–28

Cross SA, Salomao DR, Parisi JE *et al* 2003 Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-Ig. *Ann Neurol* **54**: 38–50

Croxford JL, Miller SD 2003 Immunoregulation of a viral model of multiple sclerosis using the synthetic cannabinoid R+WIN55,212. *J Clin Invest* **111**: 1231–1240

Cruikshank EK 1973 Neurological disorders in Jamaica. In: Spillane JD (ed.) *Tropical Neurology*. London: Oxford University Press, pp. 421–434

Cruikshank EK, Montgomery RD, Spillane JD 1961 Obscure neurological disorders in Jamaica. *World Neurol* **2**: 199–211

Cruickshank JK, Rudge P, Dalgleish AG *et al* 1989 Tropical spastic paraplegia and human T cell lymphotropic virus type 1 in the United Kingdom. *Brain* **112**: 1057–1090

Crusius JBA, Pena AS, van Oosten BW *et al* 1995 Interleukin-1 receptor antagonist gene polymorphism and multiple sclerosis. *Lancet* **346**: 979–980

Cruveilhier J 1829–42 *Anatomie pathologique du corps humain; descriptions avec figures lithographiées et coloriées; des diverses alterations morbides dont le corps humain est susceptible.* Paris: J.B. Baillière, 40 livraisons

Cruz BA, Queiroz ED, Nunes SV *et al* 2000 Severe Raynaud's phenomenon associated with interferon-beta therapy for multiple sclerosis: case report. *Arq Neuropsiquiatr* **58**: 556–559

Cserr HF 1984 Convection of brain interstitial fluid. In: Shapiro K, Marmarou A, Portnoy H (eds) *Hydrocephalus*. New York: Raven Press, pp. 59–68

Cserr HF, Harling-Berg CJ, Knopf PM 1992 Drainage of brain extracellular fluid into blood and deep cervical lymph and its immunological significance. *Brain Pathol* **2**: 269–276

Cua DJ, Sherlock J, Chen Y *et al* 2003 Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* **421**: 744–748

Cuadrado MJ, Khamashta MA, Ballesteros A *et al* 2000 Can neurologic manifestations of Hughes (antiphospholipid) syndrome be distinguished from multiple sclerosis? Analysis of 27 patients and review of the literature. *Medicine* **79**: 57–68

Cuddigan J, Frantz RA 1998 Pressure ulcer research: pressure ulcer treatment. A monograph from the National Pressure Ulcer Advisory Panel. Review. *Adv Wound Care* **11**: 294–300; quiz, 302.

Cui XY, Hu QD, Tekaya M *et al* 2004 NB-3/notch1 pathway via Deltex1 promotes neural progenitor cell differentiation into oligodendrocytes. *J Biol Chem* **279**: 25858–25865

Culican SM, Baumrind NL, Yamamoto M, Pearlman AL 1990 Cortical radial glia: identification in tissue culture and evidence for their transformation to astrocytes. *J Neurosci* **10**: 684–692

Cullen CG, Middleton D, Savage DA, Hawkins S 1991 HLA-DR and DQ DNA genotyping in multiple sclerosis patients in Northern Ireland. *Hum Immunol* **30**: 1–6

Cumings JN 1953 The examination of the cerebrospinal fluid and cerebral cyst fluid by paper strip electrophoresis. *J Neurol Neurosurg Psychiatry* **16**: 152–157

Cummins TR, Waxman SG 1997 Downregulation of tetrodotoxin-resistant sodium currents and upregulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. *J Neurosci* **17**: 3503–3514

Cummins TR, Black JA, Dib-Hajj SD, Waxman SG 2000 Glial-derived neurotrophic factor upregulates expression of functional SNS and NaN sodium channels and their currents in axotomized dorsal root ganglion neurons. *J Neurosci* **20**: 8754–8761

Cummins TR, Renganathan M, Stys PK *et al* 2003 The pentapeptide QYNAD does not block voltage-gated sodium channels. *Neurology* **60**: 224–229

Cunningham S, Patterson CC, McDonnell G *et al* 2005 Haplotype analysis of the preprotachykinin-1 (TAC1) gene in multiple sclerosis. *Genes Immun* **6**: 265–270

Cupples LA, Risch N, Farrer LA, Myers RH 1991 Estimation of morbid risk and age at onset with missing information. *Am J Hum Genet* **49**: 76–87

Currie S, Urich H 1974 Concurrence of multiple sclerosis and glioma. *J Neurol Neurosurg Psychiatry* **37**: 598–605

Currier RD, Haerer AF, Maydrech EF 1993 Low dose oral methotrexate treatment of multiple sclerosis: a pilot study. *J Neurol Neurosurg Psychiatry* **56**: 1217–1218

Curtius F 1933 *Multiple Sklerose und Erbanlage* Leipzig: Thieme

Curtius F, Speer H 1937 Multiple Sklerose und Erbanlage II Mittelung. *Z Neurol Psychiatr* **160**: 226–245

Custer AW, Kazarinova-Noyes K, Sakurai T *et al* 2003 The role of the ankyrin-binding protein NrCAM in node of Ranvier formation. *J Neurosci* **23**: 10032–10039

Cutter GR, Baier ML, Rudick RA *et al* 1999 Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* **122**: 871–882

Cutter NC, Scott DD, Johnson JC, Whiteneck G 2000 Gabapentin effect on spasticity in multiple sclerosis: a placebo-controlled, randomized trial. *Arch Phys Med Rehab* **81**: 164–169

Cuzner ML, Hayes GM, Newcombe J, Woodroofe MN 1988 The nature of inflammatory components during demyelination in multiple sclerosis. *J Neuroimmunol* **20**: 203–209

Cuzner ML, Gveric D, Strand C *et al* 1996 The expression of tissue-type plasminogen-activator, matrix metalloproteinases and endogenous inhibitors in the central nervous system in multiple sclerosis: comparison of stages of lesion evolution. *J Neuropathol Exp Neurol* **55**: 1194–1204

Cuzner ML, Opdenakker G 1999 Plasminogen activators and matrix metalloproteinases, mediators of extracellular proteolysis in inflammatory demyelination of the central nervous system. *J Neuroimmunol* **94**: 1–14

Dahl D, Perides G, Bignami A 1989 Axonal regeneration in old multiple sclerosis plaques: immunohistochemical study with monoclonal antibodies to phosphorylated and non-phosphorylated neurofilament proteins. *Acta Neuropathol* **79**: 154–159

Dahl OP, Aarseth JH, Myhr KM *et al* 2004 Multiple sclerosis in Nord-Trondelag County, Norway: a prevalence and incidence study. *Acta Neurol Scand* **109**: 378–384

Dai KZ, Harbo HF, Celius EG *et al* 2001 The T cell regulator gene SH2D2A contributes to the genetic susceptibility of multiple sclerosis. *Genes Immun* **2**: 263–268

Dai X, Lercher LD, Clinton PM *et al* 2003 The trophic role of oligodendrocytes in the basal forebrain. *J Neurosci* **23**: 5846–5853

Dai Y, Xu C, Holmberg M *et al* 2001a Linkage analysis suggests a region of importance for multiple sclerosis in 3p14–13. *Genes Immun* **2**: 451–454

Dai Y, Masterman T, Huang WX *et al* 2001b Analysis of an interferon-gamma gene dinucleotide-repeat polymorphism in Nordic multiple sclerosis patients. *Mult Scler* **7**: 157–163

Dai Y, Masterman T, Huang W, Hillert J 2002 Analysis of a CD40 ligand dinucleotide microsatellite in multiple sclerosis. *Eur J Immunogenet* **29**: 81–85

Dale RC, de Sousa C, Chong WK *et al* 2000 Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. *Brain* **123**: 2407–2422

Dale RC, Church AJ, Cardosa F *et al* 2001 Post-streptococcal acute disseminated encephalomyelitis with basal ganglia involvement and auto-reactive anti-basal ganglia antibodies. *Ann Neurol* **50**: 588–595

Daley D, Code C, Andersen H 1962 Disturbances of swallowing and esophageal motility in patients with multiple sclerosis. *Neurology* **12**: 250–256

D'Alfonso S, Nistico L, Zavattari P *et al* 1999 Linkage analysis of multiple sclerosis with candidate region markers in Sardinian and Continental Italian families. *Eur J Hum Genet* **7**: 377–385

D'Alfonso S, Mellai M, Giordano M *et al* 2002 Identification of single nucleotide variations in the coding and regulatory regions of the myelin-associated glycoprotein gene and study of their association with multiple sclerosis. *J Neuroimmunol* **126**: 196–204

Dalton CM, Brex PA, Jenkins R *et al* 2002a Application of the new McDonald criteria in patients with clinically isolated syndromes suggestive of multiple sclerosis. *Ann Neurol* **52**: 47–53

Dalton CM, Brex PA, Jenkins R *et al* 2002b Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **73**: 141–147

Dalton CM, Brex PA, Miszkiel KA *et al* 2003a New T2 lesions to enable an earlier diagnosis of multiple sclerosis in clinically isolated syndromes. *Ann Neurol* **53**: 673–676

Dalton CM, Brex PA, Miszkiel KM *et al* 2003b Spinal cord MRI in optic neuritis. *J Neurol Neurosurg Psychiatry* **74**: 1577–1580

Dalton CM, Chard DT, Davies GR *et al* 2004a Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. *Brain* **127**: 1101–1107

Dalton CM, Miszkiel KA, Barker GJ *et al* 2004b Effect of natalizumab on conversion of gadolinium enhancing lesions to T1 hypointense lesions in relapsing multiple sclerosis. *J Neurol* **251**: 407–413

Daly MJ, Rioux JD, Schaffner SF *et al* 2001 High-resolution haplotype structure in the human genome. *Nature Genet* **29**: 229–232

Danilov AI, Andersson M, Bavand N *et al* 2003 Nitric oxide metabolite determinations reveal continuous inflammation in multiple sclerosis. *J Neuroimmunol* **136**: 112–118

D'Arcangelo G, Grassi F, Ragozzino D *et al* 1991 Interferon inhibits synaptic potentiation in rat hippocampus. *Brain Res* **564**: 245–248

Dargent B, Paillart C, Carlier E *et al* 1994 Sodium channel internalization in developing neurons. *Neuron* **13**: 683–690

Darragh TM, Simon RP 1985 Nucleus tractus solitarius lesions elevate pulmonary arterial pressure and lymph flow. *Ann Neurol* **17**: 565–569

Das TK, Park DM 1989 Effect of treatment with botulinum toxin on spasticity. *Postgrad Med J* **65**: 208–210

DasGupta P, Haslam C, Goodwin R, Fowler CJ 1997 The 'Queen Square bladder stimulator': a device for assisting emptying of the neurogenic bladder. *Br J Urol* **80**: 234–237

DasGupta R, Wiseman O, Kanabar G, Fowler C 2004 Efficacy of sildenafil in the treatment of female sexual dysfunction due to multiple sclerosis. *J Urol* **171**: 1189–1193

Dastur OK, Singhal BS 1976 Eales' disease with neurological involvement Part II Pathology and pathogenesis. *J Neurol Sci* **27**: 323–345

Daugherty WT, Lederman RJ, Nodar RH, Conomy JP 1983 Hearing loss in multiple sclerosis. *Arch Neurol* **40**: 33–35

Davalos D, Grutzendler J, Yang G *et al* 2005 ATP mediates rapid microglial response to local brain injury *in vivo*. *Nature Neurosci* **8**: 752–758

Davenport CB 1921 Multiple sclerosis from the standpoint of geographic distribution and race. In: *Association for Research in Nervous and Mental Diseases (ARNMD)*, Vol 2. New York: Hoeber, pp. 8–19

Davenport CB 1922 Multiple sclerosis from the standpoint of geographic distribution and race. *Arch Neurol* **8**: 51–58

David E 2004 Competency, power of attorney, informed consent, wills. In: Rizzo M, Eslinger P (eds) *Principles and Practice of Behavioral Neurology and Neuropsychology*. Philadelphia, PA, WB Saunders, pp. 1071–1076

Davidoff F, DeAngelis CD, Drazen JM *et al* 2001 Sponsorship, authorship, and accountability. *N Engl J Med* **345**: 825–827

Davie CA, Hawkins CP, Barker GJ *et al* 1994 Serial proton magnetic resonance spectroscopy in acute multiple sclerosis. *Brain* **117**: 49–58

Davie CA, Barker GJ, Webb S *et al* 1995 Persistent functional deficit in multiple sclerosis and autosomal dominant cerebellar ataxia is associated with axon loss. *Brain* **118**: 1583–1592

Davie CA, Barker GJ, Webb S *et al* 1996 A proton spectroscopy study of disability in multiple sclerosis. *J Neurol* **243 (Suppl 2)**: S33

Davie CA, Barker GJ, Thompson AJ *et al* 1997 ^{1}H magnetic resonance spectroscopy of chronic cerebral white matter lesions and normal appearing white matter in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **63**: 736–742

Davies GR, Ramio-Torrenta LI, Hadjiprocopis A *et al* 2004 Evidence for grey matter MTR abnormality in relapsing remitting MS in patients with short disease duration and minimal disability. *J Neurol Neurosurg Psychiatry* **75**: 998–1002

Davies GR, Altmann DR, Hadjiprocopis A *et al* 2005 Increasing normal appearing grey and white matter magnetisation transfer ratio abnormality in early relapsing remitting MS. *J Neurol* [epub ahead of print]

Davies J 1982 Selective depression of synaptic transmission of spinal neurones in the cat by a new centrally acting muscle relaxant 5-chloro-4-(2-imidazolin-2-yl-amino)-2,1,3-benzothiadazole (DS 103–282). *Br J Pharmacol* **76**: 473–481

Davies JL, Kawaguchi Y, Bennett ST *et al* 1994 A genome-wide search for human type 1 diabetes susceptibility genes. *Nature* **371**: 130–136

Davies M, Björkman P 1988 T cell antigen receptor genes and T cell recognition. *Nature* **344**: 395–402

Davies MB, Weatherby SJ, Haq N, Ellis SJ 2000 A multiple sclerosis-like syndrome associated with glue-sniffing. *J Roy Soc Med* **93**: 313–314

Davies SE, Newcombe J, Williams SR *et al* 1995 High resolution proton NMR spectroscopy of multiple sclerosis lesions. *J Neurochem* **64**: 742–748

Davies SJ, Fitch MT, Memberg SP *et al* 1997 Regeneration of adult axons in white matter tracts of the central nervous system. *Nature* **390**: 680–683

Davis FA 1985 Neurological deficits following the hot bath test in multiple sclerosis. *J Am Med Assoc* **253**: 203

Davis FA, Jacobson S 1971 Altered thermal sensitivity in injured and demyelinated nerve: a possible model of temperature effects in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **34**: 551–561

Davis FA, Schauf CL 1981 Approaches to the development of pharmacological interventions in multiple sclerosis. *Adv Neurol* **31**: 505–510

Davis FA, Becker FO, Michael JA, Sorensen E 1970 Effect of intravenous sodium bicarbonate, disodium edetate (Na_2EDTA), and hyperventilation on visual and oculomotor signs in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **33**: 723–732

Davis FA, Michael JA, Tomaszewski JS 1973 Fluctuation of motor function in multiple sclerosis related to circadian temperature variations. *Dis Nerv Syst* **34**: 33–36

Davis FA, Schauf CL, Reed BJ, Kesler RL 1975 Experimental studies of the effects of

extrinsic factors on conduction in normal and demyelinated nerve. *J Neurol Neurosurg Psychiatry* **39**: 442–448
Davis FA, Bergen D, Schauf C *et al* 1976 Movement phosphenes in optic neuritis: a new clinical sign. *Neurology* **26**: 1100–1104
Davis FA, Stefoski D, Rush J 1990 Orally administered 4-aminopyridine improves clinical signs in multiple sclerosis. *Ann Neurol* **27**: 186–192
Davis JL, Kawaguchi Y, Bennett ST *et al* 1994 A genome-wide search for human type 1 diabetes susceptibility genes. *Nature* **371**: 130–136
Davis LE, Hersh EM, Curtis JE *et al* 1972 Immune status of patients with multiple sclerosis: analysis of primary and established immune responses in 24 patients. *Neurology* **22**: 989–997
Davis MM 2002 A new trigger for T cells. *Cell* **110**: 285–287
Davison C, Goodhart SP, Lander J 1934 Multiple sclerosis and amyotrophies. *Arch Neurol Psychiatry* **31**: 270–289
Davison K, Bagley CR 1969 Schizophrenia-like psychoses associated with organic disorders of the central nervous system: a review of the literature. *Br J Psychiatry Special Publication* **4**: 113–184
Davodeau F, Peyrat M-A, Romagné F *et al* 1995 Dual T cell receptor β chain expression on human T lymphocytes. *J Exp Med* **181**: 1391–1398
Dawson GD 1947a Cerebral responses to electrical stimulation of peripheral nerve in man. *J Neurol Neurosurg Psychiatry* **10**: 134–140
Dawson GD 1947b Investigations on a patient subject to myoclonic seizures after sensory stimulation. *J Neurol Neurosurg Psychiatry* **10**: 141–162
Dawson J 1916 The histology of disseminated sclerosis. *Trans R Soc Edinb* **50**: 517–740
Dawson MR, Polito A, Levine JM, Reynolds R 2003 NG2-expressing glial progenitor cells: an abundant and widespread population of cycling cells in the adult rat CNS. *Mol Cell Neurosci* **24**: 476–488
Day AL, Sypert GW 1976 Spinal cord sarcoidosis. *Ann Neurol* **1**: 79–85
Deacon WE, Alexander L, Siedler HD, Kurland LT 1959 Multiple sclerosis in a small New England community. *N Engl J Med* **261**: 1059–1061
Dean G 1949 Disseminated sclerosis in South Africa: its relationship to swayback and suggested treatment. *Br Med J* **1**: 842–845
Dean G 1967 Annual incidence, prevalence and mortality of MS in white South African-born and in white immigrants to South Africa. *Br Med J* **2**: 724–730
Dean G 2002 *The Turnstone*. Liverpool: Liverpool University Press
Dean G, Elian M 1997 Age at immigration to England of Asian and Caribbean immigrants and the risk of developing multiple sclerosis. *J Neurol Neurosurg Psychiatry* **63**: 565–568
Dean G, Gray R 1990 Do nurses or doctors have an increased risk of developing multiple sclerosis? *J Neurol Neurosurg Psychiatry* **53**: 899–902
Dean G, Kurtzke JF 1971 On the risk of multiple sclerosis according to age at immigration to South Africa. *Br Med J* **3**: 725–729
Dean G, McLoghlin H, Brady R *et al* 1976 Multiple sclerosis amongst immigrants in Greater London. *Br Med J* **1**: 861–864
Dean G, Grimaldi G, Kelly R, Karhausen L 1979 Multiple sclerosis is southern Europe I: Prevalence in Sicily in 1975. *J Epidemiol Community Health* **33**: 107–110
Dean G, Goodall J, Downie A 1981a The prevalence of multiple sclerosis in the Outer Hebrides compared with north-east Scotland and the Orkney and Shetland Islands. *J Epidemiol Community Health* **35**: 110–113
Dean G, Savettieri G, Giordano D *et al* 1981b The prevalence of multiple sclerosis in Sicily. II. Agrigento city. *J Epidemiol Community Health* **35**: 118–122
Dean G, McDougall EI, Elian M 1985 Multiple sclerosis in research workers studying swayback in lambs: an updated report. *J Neurol Neurosurg Psych* **48**: 859–865
Dean G, Bhigjee AIG, Bill PLA *et al* 1994 Multiple sclerosis in black South Africans and Zimbabweans. *J Neurol Neurosurg Psychiatry* **57**: 1064–1069
Dean G, Aksoy H, Akalin T *et al* 1997 Multiple sclerosis in the Turkish- and Greek-speaking communities of Cyprus. A United Nations (UNHCR) bicommunal project. *J Neurol Sci* 145: 163–168
Dean G, Elian M, de Bono AG *et al* 2002 Multiple sclerosis in Malta in 1999: an update. *J Neurol Neurosurg Psych* **73**: 256–260
De Angelis CD, Drazen JM, Frizelle FA *et al* 2005 Is this clinical trial fully registered?A statement from the International Committee of Medical Journal Editors. *N Engl J Med* **352**: 2436–2438
DeBroff DM, Donahue SP 1993 Bilateral optic neuropathy as the initial manifestation of systemic sarcoidosis. *Am J Ophthalmol* **116**: 108–110
Debruyne JC, Versijpt J, van Laere KJ *et al* 2003 PET visualization of microglia in multiple sclerosis patients using [^{11}C]PK11195. *Eur J Neurol* **10**: 257–264
De Castro S, Cartoni D, Millifiorini F *et al* 1995 Non-invasive assessment of mitoxantrone cardiotoxicity in relapsing–remitting multiple sclerosis. *J Clin Pharmacol* **35**: 627–632
Decker L, ffrench-Constant C 2004 Lipid rafts and integrin activation regulate oligodendrocyte survival. *J Neurosci* **24**: 3816–3825
Deckert-Schluter M, Schluter D, Hof H *et al* 1994 Differential expression of ICAM-1, VCAM-1 and their ligands LFA-1, Mac-1, CD43, VLA-4, and MHC class II antigens in murine Toxoplasma encephalitis: a light microscopic and ultrastructural immunohistochemical study. *J Neuropathol Exp Neurol* **53**: 457–468
D'Costa DF, Vania AK, Millac PA 1990 Multiple sclerosis associated with trismus. *Postgrad Med J* **66**: 853–854
Defer G-L, Barre J, Ladudal P *et al* 1995 Methylprednisolone infusion during acute exacerbation of MS: plasma and CSF concentrations. *Eur Neurol* **35**: 143–148
De Graaf AS 1974 Multiple sclerosis in northern Norway. *Eur Neurol* **11**: 281–295
De Groot CJ, Bergers E, Kamphorst W *et al* 2001 Post-mortem MRI-guided sampling of multiple sclerosis brain lesions: increased yield of active demyelinating and (p)reactive lesions. *Brain* **124**: 1635–1645
Deguchi K, Takeuchi H, Miki H *et al* 1992 Electrophysiological follow-up of acute and chronic experimental allergic encephalomyelitis in the Lewis rat. *Eur Arch Psych Clin Neurosci* **242**: 1–5
Dehmeshki J, Chard DT, Leary SM *et al* 2003 The normal appearing grey matter in primary progressive multiple sclerosis: a magnetisation transfer imaging study. *J Neurol* **250**: 67–74
D'Hooghe MB, Warshawski F, Ebers GS 1989 Neurogenic pulmonary edema: brain stem localization of responsible lesions. *Neurology* **39 (Suppl 1)**: 244 (abstract)
Deisenhammer F, Schellekens H, Bertolotto A 2004 Measurement of neutralizing antibodies to interferon beta in patients with multiple sclerosis. *J Neurol* **251**: II31–II39
Dejaegher L, de Bruyere M, Ketelaer P, Carton H 1983 HLA antigens and prognosis of multiple sclerosis. Part II. *J Neurol* **229**: 167–174
Dejerine J 1894 Etude sur la sclérose en plaques cerebro-spinale. A forme de sclérose laterale amyotrophique. *Rev Med (Paris)* **iv**: 193–212
De Keyser J 1988 Autoimmunity in multiple sclerosis. *Neurology* **38**: 371–374
De Keyser J, Zwanikken C, Boon M 1998 Effects of influenza vaccination and influenza illness on exacerbations in multiple sclerosis. *J Neurol Sci* **159**: 51–53
Dekker JW, Easteal S, Jakobsen IB *et al* 1993 HLA-DPB1 alleles correlate with risk for multiple sclerosis in Caucasoid and Cantonese patients lacking the high risk DQB1*0602 allele. *Tissue Antigens* **41**: 31–36
Delalande S, De Sèze J, Fauchais AL *et al* 2004 Neurologic manifestations in primary Sjögren's syndrome: a study of 82 patients. *Medicine* **83**: 280–291
De la Monte SM, Ropper AH, Dickersin GR *et al* 1986 Relapsing central and peripheral demyelinating diseases: unusual pathologic features. *Arch Neurol* **43**: 626–629
Delarasse C, Daubas P, Mars LT *et al* 2003 Myelin/oligodendrocyte glyoprotein-deficient (MOG-deficient) mice reveal lack of immune tolerance to MOG in wild-type mice. *J Clin Invest* **112**: 544–553
Delasnerie-Laupretre N, Alperovitch A 1992 Migration and age at onset of multiple sclerosis: some pitfalls of migrant studies. *Acta Neurol Scand* **85**: 408–411

De Leersnyder H, Burstin J, Ponsot G *et al* 1981 Névrites optiques chez l'enfant. *Arch Fr Pediatr* **38**: 563–572

Deloulme JC, Raponi E, Gentil BJ *et al* 2004 Nuclear expression of S100B in oligodendrocyte progenitor cells correlates with differentiation toward the oligodendroglial lineage and modulates oligodendroyctes maturation. *Mol Cell Neurosci* **27**: 453–465

DeLuca GC, Ebers GC, Esiri MM 2004 Axonal loss in multiple sclerosis: a pathological survey of the corticospinal and sensory tracts. *Brain* **127**: 1009–1018

De March AK, De Bouwerie M, Kolopp-Sarda MN *et al* 2003 Anti-myelin oligodendrocyte glycoprotein B-cell responses in multiple sclerosis. *J Neuroimmunol* **135**: 117–125

Demaree HA, DeLuca J, Gaudino EA, Diamond BJ 1999 Speed of information processing as a key deficit in multiple sclerosis: implications for rehabilitation. *J Neurol Neurosurg Psychiatry* **67**: 661–663

Deng W, Wang H, Rosenberg PA *et al* 2004 Role of metabotropic glutamate receptors in oligodendrocyte excitotoxicity and oxidative stress. *Proc Natl Acad Sci USA* **101**: 7751–7756

Denny-Brown D 1952 Multiple sclerosis: the clinical problems. *Am J Med* **12**: 501–509

Denny-Brown D, Brenner C 1944 Lesion in peripheral nerve resulting from compression by spring clip. *Arch Neurol and Psychiatry* **52**: 1–19

De Pauw A, Dejaeger E, D'hooghe B, Carton H 2002 Dysphagia in multiple sclerosis. *Clin Neurol Neurosurg* **104**: 345–351

Derbinski J, Schulte A, Kyewski B, Klein L 2001 Promiscuous gene expression in medullary thymic epithelial cells mirrors the peripheral self. *Nat Immunol* **2** 1032–1039

Derbinski J, Gäbler J, Brors B *et al* 2005 Promiscuous gene expression in thymic epithelial cells is regulated at multiple levels. *J Exp Med* **202**: 33–45

Derfuss T, Gurkov R, Bergh FT *et al* 2001 Intrathecal antibody production against *Chlamydia pneumoniae* in multiple sclerosis is part of a polyspecific immune response. *Brain* **124**: 1325–1335

De Sèze J, Stojkovic T, Destee M *et al* 2000a Paroxysmal kinesigenic choreoathetosis as a presenting symptom of multiple sclerosis. *J Neurol* **247**: 487–80

De Sèze J, Stojkovic T, Gauvrit JY *et al* 2000b Cardiac repolarization abnormalities in multiple sclerosis: spinal cord MRI correlates. *Muscle Nerve* **23**: 1284–1286

De Sèze J, Stojkovic T, Gauvrit JY *et al* 2001a Autonomic dysfunction in multiple sclerosis: cervical spinal cord atrophy correlates. *J Neurol* **248**: 297–303

De Sèze J, Devos D, Castelnovo G *et al* 2001b The prevalence of Sjogren's syndrome in patients with primary progressive multiple sclerosis. *Neurology* **57**: 1359–1363

De Sèze J, Stojkovic T, Breteau G *et al* 2001c Acute myelopathies: clinical, laboratory and outcome profiles in 79 cases. *Brain* **124**: 1509–1521

De Sèze J, Peoc'h K, Ferriby D *et al* 2002 14–3–3 protein in the cerebrospinal fluid of patients with acute transverse myelitis and multiple sclerosis. *J Neurol* **249**: 626–627

De Sèze J, Chapelotte M, Delalande D *et al* 2004 Intravenous corticosteroids in the postpartum period for reduction of acute exacerbations in multiple sclerosis. *Mult Scler* **10**: 596–597

Desmedt JE, Noel P 1973 Average somatosensory evoked potentials in the evaluation of lesions of the sensory nerves and of the central somatosensory pathway. *New Dev Electromyogr Clin Neurophysiol* **2**: 352–371

Desmond AD, Shuttleworth KED 1977 The results of urinary diversion in multiple sclerosis. *Br J Urol* **49**: 495–502

De Sousa EA, Albert RH, Kalman B 2002 Cognitive impairments in multiple sclerosis: a review. *Am J Alzheimers Dis Demen* **17**: 23–29

De Souza LH, Ashburn A 1996 Assessment of motor function in people with multiple sclerosis. *Physiother Res Int* **1**: 98–111

D'Souza SD, Antel JP, Freedman MS 1994 Cytokine induction of heat shock protein expression in human oligodendrocytes: an interleukin-1 mediated mechanism. *J Neuroimmunol* **50**: 17–24

D'Souza SD, Alinauskas KA, McCrea E *et al* 1995 Differential susceptibility of human CNS-derived cell populations to TNF-dependent and independent immune mediated injury. *J Neurosci* **15**: 7293–7300

D'Souza SD, Bonetti B, Balasingam V *et al* 1996a Multiple sclerosis: Fas signaling in oligodendrocyte cell death. *J Exp Med* **184**: 2361–2370

D'Souza SD, Alinauskas KA, Antel JP 1996b Ciliary neurotrophic factor selectively protects human oligodendrocytes from tumor necrosis factor-mediated injury. *J Neurosci Res* **43**: 289–298

DeStefano N, Matthews PM, Antel JP *et al* 1995 Chemical pathology of acute demyelinating lesions and its correlation with disability. *Ann Neurol* **38**: 901–909

DeStefano N, Matthews PM, Narayanan S *et al* 1997 Axonal dysfunction and disability in a relapse of multiple sclerosis: longitudinal study of a patient. *Neurology* **49**: 1138–1141

DeStefano N, Narayanan S, Matthews P *et al* 1999 In vivo evidence for axonal dysfunction remote from focal cerebral demyelination of the type seen in multiple sclerosis. *Brain* **122**: 1933–1939

DeStefano N, Dotti MT, Mortilla M *et al* 2000 Evidence of diffuse brain pathology and unspecific genetic characterization in a patient with an atypical form of adult-onset Krabbe disease. *J Neurol* **247**: 226–228

DeStefano N, Matthews PM, Filippi M *et al* 2003a Evidence of early cortical atrophy in MS: relevance to white matter changes and disability. *Neurology* **60**: 1157–1162

DeStefano F, Verstraeten T, Jackson LA *et al* 2003b Vaccinations and risk of central nervous system demyelinating diseases in adults. *Arch Neurol* **60**: 504–509

Detels R, Brody JF, Edgar AH 1972 Multiple sclerosis among American, Japanese and Chinese migrants to California and Washington. *J Chron Dis* **25**: 3–10

Detels R, Visscher B, Malmgrem RM *et al* 1977 Evidence for lower susceptibility to multiple sclerosis in Japanese-Americans. *Am J Epidemiol* **105**: 303–310

Detels R, Clark VA, Valdiviezo NL *et al* 1982 Factors associated with a rapid course of multiple sclerosis. *Arch Neurol* **39**: 337–341

Deuschl G, Bain P, Brin M 1998 Consensus statement of the Movement Disorder Society on Tremor. *Mov Disord* **13 (Suppl 3)**: 2–23

Devaux JJ, Alcaraz G, Grinspan J *et al* 2003a Kv3.1b is a novel component of CNS nodes. *J Neurosci* **23**: 4509–4518

Devaux JJ, Forni C, Beeton C *et al* 2003b Myelin basic protein-reactive T cells induce conduction failure *in vivo* but not *in vitro*. *NeuroReport* **14**: 317–320

Devaux JJ, Kleopa KA, Cooper EC, Scherer SS 2004 KCNQ2 is a nodal K+ channel. *J Neurosci* **24**: 1236–1244

Devey ME, Major PJ, Bleasdale-Barr KM *et al* 1990 Experimental allergic encephalomyelitis (EAE) in mice selectively bred to produce high affinity (HA) or low affinity (LA) antibody responses. *Immunology* **69**: 519–524

Devic E 1894 Myélite subaiguë compliquée de névrite optique. *Bull Med* **8**: 1033

Devinsky O, Cho E-S, Petito K, Price RW 1991 Herpes zoster myelitis. *Brain* **114**: 1181–1196

Devor M, Amir R, Rappaport ZH 2002 Pathophysiology of trigeminal neuralgia: the ignition hypothesis. *Clin J Pain* **18**: 4–13

Devos P, Destée A, Prin L, Warot P 1984 Sclérose en plaques et maladie lupique. *Rev Neurol* **140**: 513–515

Dhib-Jalbut S 2002 Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis. *Neurology* **58**: S3–S9

Dhopesh VP, Weinstein JD 1977 Spinal arteriovenous malformation simulating multiple sclerosis: importance of early diagnosis. *Dis Nerv Syst* **38**: 848–851

Di Bello IC, Dawson MR, Levine JM, Reynolds R 1999 Generation of oligodendroglial progenitors in acute inflammatory demyelinating lesions of the rat brain stem is associated with demyelination rather than inflammation. *J Neurocytol* **28**: 365–381

Di Fabio RP, Soderberg J, Choi T *et al* 1998 Extended outpatient rehabilitation: its influence on symptom frequency, fatigue, and functional status for persons with progressive multiple sclerosis. *Arch Phys Med Rehabil* **79**: 141–146

Di Majo L, Bisceglia M, Lanzillo R *et al* 2002 Aphasia as a rare presentation of

monosymptomatic demyelinating disease: case report and review of the literature. *Neurol Sci* **23**: 79–82
Di Santo JP 2001 Lung Krüppel-like factor: a quintessential player in T cell quiescence. *Nature Immunol* **2**: 667–668
Dib C, Faure S, Fizames C *et al* 1996 A comprehensive genetic map of the human genome based on 5,264 microsatellites. *Nature* **380**: 152–154
Dib-Hajj SD, Fjell J, Cummins TR *et al* 1999 Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain. *Pain* **83**: 591–600
Dichgans M, Mayer M, Uttner I *et al* 1998 The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol* **44**: 731–739
Diem R, Hobom M, Maier K *et al* 2003 Methylprednisolone increases neuronal apoptosis during autoimmune CNS inflammation by inhibition of an endogenous neuroprotective pathway. *J Neurosci* **23**: 6993–7000
Diemel LT, Copelman CA, Cuzner ML 1998 Macrophages in the CNS: friends of foe? *Neurochem Res* **23**: 341–347
van Diemen HA, van Dongen MM, Dammers JW, Polman CH 1992 Increased visual impairment after exercise (Uhthoff's phenomenon) in multiple sclerosis: therapeutic possibilities. *Eur Neurol* **32**: 231–234
van Diemen HA, Polman CH, van Dongen MM *et al* 1993 4-aminopyridine induces functional improvement in multiple sclerosis patients: a neurophysiological study. *J Neurol Sci* **116**: 220–226
DiMario FJ, Berman PH 1987 Multiple sclerosis presenting at 4 years of age: clinical and MRI correlations. *Clin Pediatr* **27**: 32–37
Dimayuga FO, Ding Q, Keller JN *et al* 2003 The neuregulin GGF2 attenuates free radical release from activated microglial cells. *J Neuroimmunol* **136**: 67–74
Ding JW, Dickie J, O'Brodovich H *et al* 1998 Inhibition of amiloride-sensitive sodium-channel activity in distal lung epithelial cells by nitric oxide. *Am J Physiol – Lung Cell Mol Physiol* **274**: L378–L387
Dinkler 1904 Zur Kasuistik der multiplen Herdsklerose des Gehirns und Rückenmarks. *Dtsch Z Nervenheilk* **26**: 233–247
Disability Committee of the Royal College of Physicians 1991 *National Concepts of Rehabilitation.* London: Royal College of Physicians Publications
Dittel BN, Stefanova I, Germain RN, Janeway CA 1999 Cross-antagonism of a T cell clone expressing two distinct T cells receptors. *Immunity* **11**: 289–298
Ditunno JF Jr, Formal CS 1994 Chronic spinal cord injury. *N Engl J Med* **330**: 550–556
Djaldetti R, Ziv I, Achiron A, Melamed E 1996 Fatigue in multiple sclerosis compared with chronic fatigue syndrome: a quantitative assessment. *Neurology* **46**: 632–635
DMKG Study Group 2003 Misoprostol in the treatment of trigeminal neuralgia associated with multiple sclerosis. *J Neurol* **250**: 542–545
Doetsch F 2003 The glial identity of neural stem cells. *Nat Neurosci* **6**: 1127–1134
Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A 1999 Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* **97**: 703–716
Dogulu CF, Kansu T 1997 Upside-down reversal of vision in multiple sclerosis. *J Neurol* **244**: 461–462
Dolei A, Serra C, Mameli G *et al* 2002 Multiple sclerosis-associated retrovirus (MSRV) in Sardinian MS patients. *Neurology* **58**: 471–473
Domeniconi M, Cao Z, Spencer T *et al* 2002 Myelin-associated glycoprotein interacts with the Nogo66 receptor to inhibit neurite outgrowth. *Neuron* **35**: 283–290
Doncel AM, Rubio A, Arroyo R *et al* 2002 Interleukin-10 polymorphisms in Spanish multiple sclerosis patients. *J Neuroimmunol* **131**: 168–172
Dong C, Juedes AE, Temann U-A *et al* 2001 ICOS co-stimulatory receptor is essential for T-cell activation and function. *Nature* **409**: 70–101
Dong-Si T, Weber J, Liu YB *et al* 2004 Increased prevalence of and gene transcription by *Chlamydia pneumoniae* in cerebrospinal fluid of patients with relapsing–remitting multiple sclerosis. *J Neurol* **251**: 542–547
Donnadieu E, Revy P, Trautmann A 2001 Imaging T cell antigen recognition and comparing immunological and neuronal synapses. *Immunol* **103**: 417–425
Donnan PT, Parratt JDE, Wilson SV *et al* 2005 Multiple sclerosis in Tayside, Scotland: detection of clusters using a spatial scan statistic. *Mult Scler* **11**: 403–408
Dooley JM, Wright BA 1985 Adrenoleukodystrophy mimicking multiple sclerosis. *Can J Neurol Sci* **12**: 73–74
Doolittle TH, Myers RH, Lehrich JR *et al* 1990 Multiple sclerosis sibling pairs: clustered onset and familial predisposition. *Neurology* **40**: 937–950
Doraiswamy PM, Rao SM 2004 Treating cognitive deficits in multiple sclerosis: are we there yet? *Neurology* **63**: 1552–1553
Dore-Duffy P, Donaldson JO, Rothman BL, Zurier RB 1982 Antinuclear antibodies in multiple sclerosis. *Arch Neurol* **39**: 504–506
Dore-Duffy P, Ho SY, Donovan C 1991 Cerebrospinal fluid eicosanoid levels: endogenous PGD2 and LTC4 synthesis by antigen-presenting cells that migrate to the central nervous system. *Neurology* **41**: 322–324
Dore-Duffy P, Washington R, Dragovic L 1993 Expression of endothelial cell activation antigens in microvessels from patients with multiple sclerosis. *Adv Exper Med Biol* **331**: 243–248
Dore-Duffy P, Newman W, Balabanov R *et al* 1995 Circulating, soluble adhesion proteins in cerebrospinal fluid and serum of patients with multiple sclerosis: correlation with clinical activity. *Ann Neurol* **37**: 55–62
Dornmair K, Goebels N, Weltzien H-U *et al* 2003 T cell-mediated autoimmunity: novel techniques to characterize autoreactive T cell receptors. *Am J Pathol* **163**: 1215–1226
Dorr J, Bechmann I, Waiczies S *et al* 2002 Lack of tumor necrosis factor-related apoptosis-inducing ligand but presence of its receptors in the human brain. *J Neurosci* **22**: RC209
Doty RL, Li C, Mannon LJ, Yousem DM 1998 Olfactory dysfunction in multiple sclerosis: relation to plaque load in inferior frontal and temporal lobes. *Ann N Y Acad Sci* **855**: 781–786
Doty RL, Li C, Mannon LJ, Yousem DM 1999 Olfactory dysfunction in multiple sclerosis: relation to longitudinal changes in plaque numbers in central olfactory structures. *Neurology* **53**: 880–882
Douglass LH, Jorgensen CL 1948 Pregnancy and multiple sclerosis. *Am J Obstetr Gynecol* **55**: 332–336
Dousset V, Rosman R, Ramer KN *et al* 1992 Experimental allergic encephalomyelitis and multiple sclerosis lesion characterization with magnetization transfer imaging. *Radiology* **182**: 483–491
Dousset V, Brochet B, Vital F, Nagem F, Bonnet J, Caille JM 1994 Imaging including diffusion and magnetization transfer of chronic relapsing experimental encephalomyelitis – correlation with immunological and pathological data. *Proc Soc Magn Reson* **2**: 1401 (abstract)
Dousset V, Brochet B, Vital A *et al* 1995 Lysolecithin-induced demyelination in primates: preliminary *in vivo* study with MR and magnetization transfer. *Am J Neuroradiol* **16**: 225–231
Dousset V, Delalande C, Ballarino L *et al* 1999 In vivo macrophage activity imaging in the central nervous system detected by magnetic resonance. *Magn Reson Med* **41**: 329–333
Dousset V, Brochet B, Cailee J-M, Petry K 2000 MS lesions enhancement with ultrasmall particle iron oxide: the first phase II study. *Rev Neurol* **156**: 3S40
Dowling PC, Bosch VV, Cook SD 1980 Possible beneficial effect of high dose intravenous steroid therapy in acute demyelinating disease and transverse myelitis. *J Neurol Neurosurg Psychiatry* **30**: 33–36
Dowling P, Shang G, Raval S *et al* 1996 Involvement of the CD95 (APO-1/Fas) receptor/ligand system in multiple sclerosis brain. *J Exp Med* **184**: 1513–1518
Downie AW 1984 The Chief Scientist Report. Multiple sclerosis in North East Scotland. *Health Bull Edinb* **42**: 151–156
Drazen JM 2005 Patients at risk. *N Engl J Med* **353**: 417
Dressnandt J, Conrad B 1996 Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* **60**: 168–173
Dreyfus GL, Mayer K 1929 Vier Jähne Malariabehandlung der multiplen Sklerose. *Dtsch Z Nervenheilk* **111**: 68–98

Droogan AG, Kirk CW, Hawkins SA *et al* 1996 T-cell receptor alpha, beta, gamma, and delta chain gene microsatellites show no association with multiple sclerosis. *Neurology* **47**: 1049–1053

Droogan AG, Crockard AD, McMillan SA, Hawkins SA 1998 Effects of intravenous methylprednisolone therapy on leukocyte and soluble adhesion molecule expression in MS. *Neurology* **50**: 224–229

Drouin E, Nataf S, Lande G, Louboutin JP 1998 Abnormalities of cardiac repolarization in multiple sclerosis: relationship with a model of allergic encephalomyelitis in rat. *Muscle & Nerve* **21**: 940–942

Drulovic B, Ribaric-Jankes K, Kostic VE, Sternic N 1993 Sudden hearing loss as the initial monosymptom of multiple sclerosis. *Neurology* **43**: 2703–2705

Drulovic J, Dozic S, Levic Z *et al* 1998 Unusual association of multiple sclerosis and tomaculous neuropathy. *J Neurol Sci* **157**: 217–222

Du C, Yao S, Ljunggren-Rose Å, Sriram S 2002 *Chlamydia pneumoniae* infection of the central nervous system worsens experimental allergic encephalitis. *J Exp Med* **196**: 1639–1644

Dubois BD, Masure S, Hurtenbach U *et al* 1999 Resistance of young gelatinase B-deficient mice to experimental autoimmune encephalomyelitis and necrotizing tail lesions. *J Clin Invest* **104**: 1507–1515

Dubois BD, Keenan E, Porter BE *et al* 2003 Interferon beta in multiple sclerosis: experience in a British specialist multiple sclerosis centre. *J Neurol Neurosurg Psychiatry* **74**: 946–949

Dubois-Dalcq M, Niedieck B, Buyse M 1970 Action of anti-cerebroside sera on myelinated nervous tissue cultures. *Patol Eur* **5**: 331–347

Dubois-Dalcq M, Schumacher G, Sever JL 1973 Acute multiple sclerosis: electron-microscopic evidence for and against a viral agent in the plaques. *Lancet* **ii**: 1408–1411

Duchen MR 2000 Mitochondria and calcium: from cell signalling to cell death. *J Physiol* **529**: 57–68

Duckworth D 1885 Disseminated cerebro-spinal sclerosis in an early stage affecting exclusively the right extremities. *Lancet* **i**: 879–880

Duclos P 1992 Adverse events after hepatitis B vaccination. *Can Med Assoc J* **147**: 1023–1026

Duclos P 2003 Safety of immunization and adverse events following vaccination against hepatitis B. *Expert Opin Drug Safety* **2**: 225–231

Duda PW, Schmied MC, Cook SL *et al* 2000 Glatiramer acetate (Copaxone) induces degenerate, Th2-polarized immune responses in patients with multiple sclerosis. *J Clin Invest* **105**: 967–976

Dufour A, Corsini E, Gelati M *et al* 2000 In vitro glatiramer acetate treatment of brain endothelium does not reduce adhesion phenomena. *Ann Neurol* **47**: 680–682

Dugandzija-Novakovic S, Koszowski AG, Levinson SR, Shrager P 1995a Clustering of Na+ channels and node of Ranvier formation in remyelinating axons. *J Neurosci* **15**: 492–503

Dugandzija-Novakovic S, Shrager P 1995b Survival, development, and electrical activity of central nervous system myelinated axons exposed to tumor necrosis factor in vitro. *J Neurosci Res* **40**: 117–126

Dukart G, JS B 1984 An overview of cardiac episodes following mitoxantrone administration. *Cancer Treat Symp* **3**: 35–41

Dumas M, Jauberteau-Marchan MO 2000 The protective role of Langerhans' cells and sunlight in multiple sclerosis. *Med Hypotheses* **55**: 517–520

Duncan SR, Scott S, Duncan CJ 2005 Reappraisal of the historical selective pressures for the CCR5-Δ32 mutation. *J Med Genet* **42**: 205–208

Dunn V, Bale JF, Zimmerman RA *et al* 1986 MRI in children with postinfectious disseminated encephalomyelitis. *Mag Reson Imag* **4**: 25–32

Dupont B (ed.) 1992 Nomenclature for the factors of the HLA system, 1991. *Tissue Antigens* **39**: 1–13

Dupont B, Lisak RP, Jersild C *et al* 1977 HLA antigens in black Americans with multiple sclerosis. *Transplantation Proc* **9 (Suppl 1)**: 181–185

Dupont RM, Jernigan TL, Butters N *et al* 1990 Subcortical abnormalities detected in bipolar affective disorder using magnetic resonance imaging: clinical and neuropsychological significance. *Arch Gen Psychiatry* **47**: 55–59

Dupree JL, Girault J-A, Popko B 1999 Axo-glial interactions regulate the localization of axonal paranodal proteins. *J Cell Biol* **147**: 1145–1151

Duquette P, Decary F, Pleines J *et al* 1985 Clinical sub-groups of multiple sclerosis in relation to HLA: DR alleles as possible markers of disease progression. *Can J Neurol Sci* **12**: 106–110

Duquette P, Murray TJ, Pleines J *et al* 1987 Multiple sclerosis in childhood: clinical profile in 125 patients. *J Pediatr* **111**: 359–363

Durelli L, Cocito D, Riccio A *et al* 1986 High-dose intravenous methylprednisolone in the treatment of multiple sclerosis: clinical-immunological correlations. *Neurology* **36**: 238–243

Durelli L, Bongioanni MR, Cavallo R *et al* 1994 Chronic systemic high-dose recombinant interferon alfa-2a reduces exacerbation rate, MRI signs of disease activity, and lymphocyte interferon gamma production in relapsing–remitting multiple sclerosis. *Neurology* **44**: 406–413

Durelli L, Bongioanni MR, Ferrero B *et al* 1996 Interferon alpha-2a treatment of relapsing–remitting multiple sclerosis: disease activity resumes after stopping treatment. *Neurology* **47**: 123–129

Durelli L, Bongioanni MR, Ferrero B *et al* 1998 Interferon treatment for multiple sclerosis: autoimmune complications may be lethal. *Neurology* **50**: 570–571

Durelli L, Ferrero B, Oggero A *et al* 1999 Autoimmune events during interferon beta-1b treatment for multiple sclerosis. *J Neurol Sci* **162:** 74–83

Durelli L, Verdun E, Barbero P *et al* 2002 Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet* **359**: 1453–1460

Dustin ML, Colman DR 2002 Neural and immunological synaptic relations. *Science* **298**: 785–789

Dutton RW, Bradley LM, Swain SL 1998 T cell memory. *Annu Rev Immunol* **16**: 201–223

DuVall MD, Zhu S, Fuller CM, Matalon S 1998 Peroxynitrite inhibits amiloride-sensitive Na+ currents in Xenopus oocytes expressing alpha beta gamma-rENaC. *Am J Physiol* **274**: C1417–C1423

Duvefelt K, Anderson M, Fogdell-Hahn A, Hillert J 2004 A NOTCH4 association with multiple sclerosis is secondary to HLA-DR*1501. *Tissue Antigens* **63**: 13–20

Dworkin RH, Bates D, Millar JHD, Paty DW 1984 Linoleic acid and multiple sclerosis: a reanalysis of three double blind trials. *Neurology* **34**: 1441–1445

Dyment DA, Ebers GC 2002 An array of sunshine in multiple sclerosis. *N Engl J Med* **347**: 1445–1447

Dyment DA, Willer CJ, Scott B *et al* 2001 Genetic susceptibility to MS: a second stage analysis in Canadian MS families. *Neurogenetics* **3**: 145–151

Dyment DA, Cader MZ, Wiler CJ *et al* 2002a A multigenerational family with multiple sclerosis. *Brain* **125**: 1474–1482

Dyment DA, Steckley JL, Willer CJ *et al* 2002b No evidence to support CTLA-4 as a susceptibility gene in MS families: the Canadian collaborative study. *J Neuroimmunol* **123**: 193–198

Dyment DA, Steckley JL, Morrison K *et al* 2004a TCR beta polymorphisms and multiple sclerosis. *Genes Immun* **5**: 337–342

Dyment DA, Sadovnick AD, Willer CJ *et al* 2004b An extended genome scan in 442 Canadian multiple sclerosis-affected sibships: a report from the Canadian collaborative Study Group. *Hum Mol Genet* **13**: 1005–1015

Dyment DA, Herrera BM, Cader MZ *et al* 2005 Complex interactions among MHC haplotypes in multiple sclerosis: susceptibility and resistance *Hum Mol Genet* **14**: 2019–2026

Dziembowska M, Tham TN, Lau P *et al* 2005 A role for CXCR4 signaling in survival and migration of neural and oligodendrocyte precursors. *Glia* **50**: 258–269

Earl CJ 1964 Some aspects of optic atrophy. *Trans Ophthalmol Soc UK* **84**: 215–226

Earl CJ, Martin B 1967 Prognosis in optic neuritis related to age. *Lancet* **i**: 74–76

Eastman R, Sheridan J, Poskanzer DC 1973 Multiple sclerosis clustering in a small

Massachusetts community, with possible common exposure 23 years before onset. *New Engl J Med* **289**: 793–794

Eaves IA, Merriman TR, Barber RA *et al* 2000 The genetically isolated populations of Finland and Sardinia may not be a panacea for linkage disequilibrium mapping of common disease genes. *Nature Genet* **25**: 320–323

Ebers G 2000 The natural history of multiple sclerosis. *Neurol Sci* **21 (Suppl)**: 815–817

Ebers GC 1985a Osler and neurology. *Can J Neurol Sci* **12**: 236–242

Ebers GC 1985b Optic neuritis and multiple sclerosis. *Arch Neurol* **42**: 702–704

Ebers GC 1998 Natural history of multiple sclerosis. In: Compston A, Ebers G, Lassmann H *et al* (eds) *McAlpine's Multiple Sclerosis, 3rd edn.* London: Churchill Livingstone, pp. 191–221

Ebers GC, Cripps J, Rudd A 1982a Birth order and multiple sclerosis. *Acta Neurol Scand* **66**: 342–346

Ebers GC, Paty DW, Stiller CR *et al* 1982b HLA typing and sibling pairs with multiple sclerosis. *Lancet* **ii**: 88–90

Ebers GC, Bulman DE, Sadovnick AD *et al* 1986 A population based study of multiple sclerosis in twins. *N Engl J Med* **315**: 1638–1642

Ebers GC, Sadovnick AD, Risch NJ 1995 A genetic basis for familial aggregation in multiple sclerosis. *Nature* **377**: 150–151

Ebers GC, Kukay K, Bulman D *et al* 1996 A full genome search in multiple sclerosis. *Nature Genet* **13**: 472–476

Ebers GC, Yee IM, Sadovnick AD, Duquette P 2000a Conjugal multiple sclerosis: population-based prevalence and recurrence risks in offspring. Canadian Collaborative Study Group. *Ann Neurol* **48**: 927–931

Ebers GC, Koopman WJ, Hader W *et al* 2000b The natural history of multiple sclerosis: a geographically based study. *Brain* **123**: 641–649

Ebers GC, Sadovnick AD, Dyment DA *et al* 2004 Parent-of-origin effect in multiple sclerosis: observations in half-siblings. *Lancet* **363**: 1773–1774

Edan G, Miller DH, Clanet M *et al* 1997 Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicenter study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* **62**: 112–118

Eddleston M, Mucke L 1993 Molecular profile of reactive astrocytes – implications for their role in neurologic disease. *Neuroscience* **54**: 15–36

Edgley K, Sullivan M, Dehoux E 1991 A survey of multiple sclerosis: determinants of employment status. *Can J Rehab* **4**: 127–132

Edland A, Nyland H, Riise T, Larsen JP 1996 Epidemiology of multiple sclerosis in the county of Vestfold, eastern Norway: incidence and prevalence calculations. *Acta Neurol Scand* **93**: 104–109

Edmund J, Fog T 1955 Visual and motor instability in multiple sclerosis. *Arch Neurol Psychiatry* **73**: 316–323

Edwards BA 1889 *De l'hemiplegie dans quelques affections nerveuses.* Paris: Bureaux du Progres & A. Delahaye et Lecrosnier

Edwards LJ, Constantinescu CS 2004 A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. *Mult Scler* **10**: 575–581

Edwards S, Zvartau M, Clarke H *et al* 1998 Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **64**: 736–741

Egen JG, Kuhns MS, Allison JP 2002 CTLA-4: new insights into its biological function and use in tumor immunotherapy. *Nat Immunol* **3**: 611–618

Eglitis MA, Mezey E 1997 Hematopoietic cells differentiate into both microglia and macroglia in the brains of adult mice. *Proc Natl Acad Sci USA* **94**: 4080–4085

Ehde D, Gibbons L, Chwastiak L *et al* 2003 Chronic pain in a large community sample of persons with multiple sclerosis. *Mult Scler* **9**: 605–611

Ehling R, Gassner Ch, Lutterotti A *et al* 2004 Genetic variants in the tumor necrosis factor receptor II gene in patients with multiple sclerosis. *Tissue Antigens* **63**: 28–33

Ehrhard PB, Erb P, Graumann U, Otten U 1993 Expression of nerve growth factor and nerve growth factor receptor tyrosine kinase Trk in activated CD4-positive T-cell clones. *Proc Natl Acad Sci USA* **90**: 10984–10988

Ehrlich P, Morgenroth J 1901 Über Hämolysine: Fünfte Mitteilung. Berlin. *Klin Wschr* **38**: 251–256

Eichler FS, Barker PB, Cox C *et al* 2002 Proton MR spectroscopic imaging predicts lesion progression on MRI in X-linked adrenoleucodystrophy. *Neurology* **58**: 901–907

Eichorst H 1896 Über infantile und hereditare multiple Sklerose. *Virchow's Arch Pathologie Anat Berl* **146**: 173–192

Eickhoff K, Heipertz R 1979 The activity of 2', 3'-cyclic nucleotide 3'-phosphohydrolase in human cerebrospinal fluid. *Clin Chim Acta* **92**: 303–305

Eidelberg D, Newton MR, Johnson G *et al* 1988 Chronic unilateral optic neuropathy: a magnetic resonance study. *Ann Neurol* **24**: 3–11

Eikelenboom MJ, Petzold A, Lazeron RH *et al* 2003 Multiple sclerosis: neurofilament light chain antibodies are correlated to cerebral atrophy. *Neurology* **60**: 219–223

Eisen A, Odusote K 1980 Central and peripheral conduction times in multiple sclerosis. *Electroencephalogr Clin Neurophysiol* **48**: 253–265

Ekbom K 1966 Familial multiple sclerosis associated with narcolepsy. *Arch Neurol* **15**: 337–344

Eldridge R, McFarland H, Sever J *et al* 1978 Familial multiple sclerosis: clinical, histocompatibility, and viral serological studies. *Ann Neurol* **3**: 72–80

Eldridge R, Anayiotos CP, Schlesinger S *et al* 1984 Hereditary adult-onset leukodystrophy simulating chronic progressive multiple sclerosis. *N Engl J Med* **311**: 948–953

Elian M, Dean G 1977 Multiple sclerosis and epilepsy. In: Perry JK (ed.) *Epilepsy, the 8th International Symposium*. New York: Raven Press, pp. 341–344

Elian M, Dean G 1987 Multiple sclerosis among United Kingdom born children of immigrants from the West Indies. *J Neurol Neurosurg Psychiatry* **50**: 327–332

Elian M, Alonso A, Awad J *et al* 1987 HLA associations with multiple sclerosis in Sicily and Malta. *Disease Markers* **5**: 89–99

Elian M, Nightingale S, Dean G 1990 Multiple sclerosis among United Kingdom-born children of immigrants from the Indian subcontinent, Africa and the West Indies. *J Neurol Neurosurg Psychiatry* **53**: 906–911

Elliott JI, Douek DC, Altmann DM 1996 Mice lacking $\alpha\beta^+$ T cells are resistant to the induction of experimental autoimmune encephalomyelitis. *J Neuroimmunol* **70**: 139–144

Ellis H 1998 MS. *Lancet* **351**: 1295

Ellison GW, Myers LW, Mickey MR *et al* 1989 A placebo-controlled, randomised, double-masked, variable dosage, clinical trial of azathioprine with and without methylprednisolone in multiple sclerosis. *Neurology* **39**: 1018–1026

Elovaara I, Lällä M, Spåre E *et al* 1998 Methylprednisolone reduces adhesion molecules in blood and cerebrospinal fluid in patients with MS. *Neurology* **51**: 1703–1708

Elovaara I, Ukkonen M, Leppakynnas M *et al* 2000 Adhesion molecules in multiple sclerosis: relation to subtypes of disease and methylprednisolone therapy. *Arch Neurol* **57**: 546–551

Elrington GM, Bateman DE, Jeffrey MJ, Lawton NF 1989 Adrenoleukodystrophy: heterogeneity in two brothers. *J Neurol Neurosurg Psychiatry* **52**: 310–313

Encinas JA, Lees MB, Sobel RA *et al* 1996 Genetic analysis of susceptibility to experimental autoimmune encephalomyelitis in a cross between SJL/J and B10.S mice. *J Immunol* **157**: 2186–2192

Encinas JA, Wicker LS, Peterson LB *et al* 1999 QTL influencing autoimmune diabetes and encephalomyelitis map to a 0.15-cM region containing *IL2*. *Nature Genet* **21**: 158–160

Encinas JA, Lees MB, Sobel RA *et al* 2001 Identification of genetic loci associated with paralysis, inflammation and weight loss in mouse experimental autoimmune encephalomyelitis. *Int Immunol* **13**: 257–264

Eng LF, Ghirnikar RS 1994 GFAP and astrogliosis. *Brain Pathol* **4**: 229–237

Engel U, Wolswijk G 1996 Oligodendrocyte-type-2 astrocyte (0–2a) progenitor cells derived from adult-rat spinal-cord – *in-vitro* characteristics and response to PDGF, bFGF and NT-3. *Glia* **16**: 16–26

van Engelen BGM, Hommes OR, Pinckers A *et al* 1992 Improved vision after intravenous immunoglobulin in stable demyelinating optic neuritis. *Ann Neurol* **32**: 835–836

Engelhardt B, Wolburg H 2004 Transendothelial migration of leukocytes: through the front door or around the side of the house? *Eur J Immunol* **34**: 2955–2963

Engelhardt B, Laschinger M, Schulz M *et al* 1998 The development of experimental autoimmune encephalomyelitis in the mouse requires alpha4-integrin but not alpha4beta7-integrin. *J Clin Invest* **102**: 2096–2105

Engelken JD, Yuh WTC, Carter KD, Nerad JA 1992 Optic nerve sarcoidosis: MR findings. *Am J Neuroradiol* **13**: 228–230

Engell T 1986 Neurological disease activity in multiple sclerosis patients with periphlebitis retinae. *Acta Neurol Scand* **73**: 168–172

Engell T 1988 A clinico-pathoanatomical study of multiple sclerosis diagnosis. *Acta Neurol Scand* **78**: 29–44

Engell T 1989 A clinical patho-anatomical study of clinically silent multiple sclerosis. *Acta Neurol Scand* **79**: 428–430

Engell T, Andersen PK 1982 The frequency of periphlebitis retinae in multiple sclerosis. *Acta Neurol Scand* **65**: 601–608

Engell T, Raus NE, Thompsen M, Platz M 1982 HLA and heterogeneity of multiple sclerosis. *Neurology* **32**: 1043–1046

Engell T, Hvidberg A, Uhrenholdt A 1984 Multiple sclerosis: periphlebitis retinalis et cerebrospinalis. A correlation between periphlebitis retinalis and abnormal technetium brain scintigraphy. *Acta Neurol Scand* **69**: 293–297

Engell T, Jensen OA, Klinken L 1985 Periphlebitis retinae in multiple sclerosis: a histopathological study of 2 cases. *Acta Ophthalmol* **68**: 83–88

England JD, Gamboni F, Levinson SR, Finger TE 1990 Changed distribution of sodium channels along demyelinated axons. *Proc Natl Acad Sci USA* **87**: 6777–6780

England JD, Gamboni F, Levinson SR 1991 Increased numbers of sodium channels form along demyelinated axons. *Brain Res* **548**: 334–337

England JD, Levinson SR, Shrager P 1996 Immunocytochemical investigations of sodium channels along nodal and internodal portions of demyelinated axons. *Microsc Res Techn* **34**: 445–451

England S, Bevan S, Docherty RJ 1996 PGE2 modulates the tetrodotoxin-resistant sodium current in neonatal rat dorsal root ganglion neurones via the cyclic AMP-protein kinase A cascade. *J Physiol* **495**: 429–440

Enzinger C, Ropele S, Smith S *et al* 2004a Accelerated evolution of brain atrophy and 'black holes' in MS patients with *APOE*-ε4. *Ann Neurol* **55**: 563–569

Enzinger C, Ropele S, Strasser-Fuchs S *et al* 2004b Lower levels of N-acetylaspartate in multiple sclerosis patients with the apolipoprotein E epsilon4 allele. *Arch Neurol* **61**: 296

Eoli M, Wood NW, Kellar-Wood H *et al* 1994a No linkage between multiple sclerosis and the T cell receptor alpha chain locus. *J Neurol Sci* **14**: 32–37

Eoli M, Pandolfo M, Milanese C *et al* 1994b The myelin basic protein gene is not a major susceptibility locus for multiple sclerosis in Italian patients. *J Neurol* **241**: 615–619

Epplen C, Jackel S, Santos EJM *et al* 1997 Genetic predisposition to multiple sclerosis as revealed by immunoprinting. *Ann Neurol* **41**: 341–352

Eraksoy M, Kürtüncü M, Akman-Demir G *et al* 2003a A whole genome screen for linkage in Turkish multiple sclerosis. *J Neuroimmunol* **143**: 17–24

Eraksoy M, Hensiek A, Kürtüncü M *et al* 2003b A genome screen for linkage disequilibrium in Turkish multiple sclerosis. *J Neuroimmunol* **143**: 129–132

Erben S 1898 Zur Histologie und Pathologie der inselförmigen Sklerose. *Neurol Centralb* **14**: 626–635

Erdem E, Carlier R, Idir ABC *et al* 1993a Gadolinium-enhanced MRI in central nervous system Behçet's disease. *Neuroradiology* **35**: 142–144

Erdem E, Carlier R, Delvalle A, Caquet R, Etienne JP, Doyon D 1993b Gadolinium enhanced MRI in Whipple's disease. *Neuroradiology* **35**: 581–583

Erdemli G, Krnjevic K 1995 Nitric oxide tonically depresses a voltage- and Ca-dependent outward current in hippocampal slices. *Neurosci Lett* **201**: 57–60

Eriksson M, Ben-Menachem E, Andersen O 2002 Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. *Mult Scler* **8**: 495–499

Eriksson M, Andersen O, Runmarker B 2003 Long-term follow-up of patients with clinically isolated syndromes, relapsing–remitting and secondary progressive multiple sclerosis. *Mult Scler* **9**: 260–274

Eriksson PS, Perfilieva E, Bjork-Eriksson T *et al* 1998 Neurogenesis in the adult human hippocampus. *Nature Med* **4**: 1313–1317

Esiri MM 1977 Immunoglobulin-containing cells in multiple sclerosis plaques. *Lancet* **ii**: 478–480

Esiri MM 1980 Multiple sclerosis: a quantitative and qualitative study of immunoglobulin-containing cells in the central nervous system. *Neuropathol Appl Neurobiol* **6**: 9–21

Esiri MM, Reading MC 1987 Macrophage populations associated with multiple sclerosis plaques. *Neuropathol Appl Neurobiol* **13**: 451–465

Esiri MM, Reading MC, Squier MV, Hughes JT 1989 Immunocytochemical characterization of the macrophage and lymphocyte infiltrate in the brain in six cases of human encephalitis. *Neuropathol Appl Neurobiol* **15**: 289–305

Espey MG, Chernyshev ON, Reinhard JF *et al* 1997 Activated human microglia produce the excitotoxin quinolinic acid. *NeuroReport* **8**: 431–434

Estes ML, Rudick RA, Barnett GH, Ransohoff RM 1990 Stereotactic biopsy of an active multiple sclerosis lesion: immunocytochemical analysis and neuropathologic correlation with magnetic resonance imaging. *Arch Neurol* **47**: 1299–1303

Etus V, Akansel G, Ilbay K *et al* 2002 Multiple sclerosis and coexisting extramedullary spinal cord tumour: a case report. *Neurol Sci* **23**: 119–122

Eugster HP, Frei K, Kopf M *et al* 1998 IL-6-deficient mice resist myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. *Eur J Immunol* **28**: 2178–2187

Eugster HP, Frei K, Bachmann R *et al* 1999 Severity of symptoms and demyelination in MOG-induced EAE depends on TNFR1. *Eur J Immunol* **29**: 626–632

European Study Group in Interferon Beta-1b in Secondary Progressive MS 1998 Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* **352**: 1491–1497

Evangelou N, Jackson M, Beeson D, Palace J 1999 Association of the APOE e4 allele with disease activity in multiple sclerosis. *J Neurol Neurosurg Psych* **67**: 203–205

Evangelou N, Konz D, Esiri MM *et al* 2000a Regional axonal loss in the corpus callosum correlates with cerebral white matter lesion volume and distribution in multiple sclerosis. *Brain* **123**: 1845–1849

Evangelou N, Esiri MM, Smith S *et al* 2000b Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis. *Ann Neurol* **47**: 391–395

Evangelou N, Konz D, Esiri MM *et al* 2001 Size-selective neuronal changes in the anterior optic pathways suggest a differential susceptibility to injury in multiple sclerosis. *Brain* **124**: 1813–1820

Evangelou N, DeLuca GC, Owens T, Esiri MM 2005 Pathological study of spinal cord atrophy in multiple sclerosis suggests limited role of focal lesions. *Brain* **128**: 29–34

Evans AC, Frank JA, Antel JP, Miller DH 1997 The role of MRI in clinical trials of multiple sclerosis: comparison of image processing techniques. *Ann Neurol* **41**: 125–132

Evans AR, Vasko MR, Nicol GD 1999 The cAMP transduction cascade mediates the PGE2-induced inhibition of potassium currents in rat sensory neurones. *J Physiol* **516**: 163–178

Evans CF, Horwitz MB, Hobbs MV, Oldstone MB 1996 Viral infection of transgenic mice expressing a viral protein in oligodendrocytes leads to chronic central nervous system autoimmune disease. *J Exp Med* **184**: 2371–2384

Evans M, Kaufman M 1981 Establishment in culture of pluripotent cells from mouse embryos. *Nature* **292**: 154–156

Evron S, Brenner T, Abramsky O 1984 Suppressive effect of pregnancy on the development of experimental allergic encephalomyelitis in rabbits. *Am J Reprod Immunol* **5**: 109–113

Expanded Programme on Immunization (EPI) 1997 Lack of evidence that hepatitis B vaccine causes multiple sclerosis. *Wkly Epidemiol Rec* **72**: 149–152

Eyssette M, Rohmer F, Serratrice G, Warter JM, Boisson D 1988 Multi-centre, double-blind trial of a novel antispastic agent, tizanidine, in spasticity associated with multiple sclerosis. *Curr Med Res Opin* **10**: 699–708

Fabry Z, Raine CS, Hart MN 1994 Nervous tissue as an immune compartment: the dialect of the immune response in the CNS. *Immunol Today* **15**: 218–224

Falcone M, Rajan AJ, Bloom BR, Brosnan CF 1998 A critical role for IL-4 in regulating disease severity in experimental allergic encephalomyelitis as demonstrated in IL-4-deficient C57BL/6 mice and BALB/c mice. *J Immunol* **160**: 4822–4830

Fallis RJ, McFarlin DE 1989 Chronic relapsing experimental allergic encephalomyelitis: cytotoxicity effected by a class II-restricted T cell line specific for an encephalitogenic epitope. *J Immunol* **143**: 2160–2165

Fallis RJ, Powers ML, Sy M-S, Weiner HL 1987 Adoptive transfer of murine chronic relapsing autoimmune encephalomyelitis: analysis of basic protein-reactive cells in lymphoid organs and nervous system of donor and recipient animals. *J Neuroimmunol* **14**: 205–219

Fallowfield L, Jenkins V 2004 Communicating sad, bad, and difficult news in medicine. *Lancet* **363**: 312–319

Fancy SP, Zhao C, Franklin RJ 2004 Increased expressionh of Nkx2.2 and Olig2 identifies reactive oligodendrocyte progenitor cells responding to demyelination in the adult CNS. *Mol Cell Neurosci* 27: 247–254

Farina C, Then Bergh F, Albrecht H *et al* 2001 Treatment of multiple sclerosis with Copaxone (COP): Elispot assay detects COP-induced interleukin-4 and interferon-gamma response in blood cells. *Brain* **124**: 705–719

Farina C, Vargas V, Heydari N *et al* 2002 Treatment with glatiramer acetate induces specific IgG4 antibodies in multiple sclerosis patients. *J Neuroimmunol* **123**: 188–192

Farina L, Bizzi A, Finochiarro G *et al* 2000 MR imaging and proton MR spectroscopy in adult Krabbe disease. *Am J Neuroradiol* **21**: 1478–1482

Fassas A, Kimiskidis V 2003 Stem cell transplantation for multiple sclerosis: what is the evidence? *Blood Rev* **17**: 233–240

Fassas A, Anagnostopoulos A, Kazis A *et al* 2000 Autologous stem cell transplantation in progressive multiple sclerosis—an interim analysis of efficacy. *J Clin Immunol* **20**: 24–30

Fassas A, Passweg JR, Anagnostopoulos A *et al* 2002 Hematopoietic stem cell transplantation for multiple sclerosis: a retrospective multicenter study. *J Neurol* **249**: 1088–1097

Fatemi A, Barker PB, Ulu AM *et al* 2003 MRI and proton MRSI in women heterozygous for X-linked adrenoleucodystrophy. *Neurology* **60**: 1301–1307

Fatigue Guidelines Development Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines 1998 *Fatigue and Multiple Sclerosis: Evidence-based Management Strategies for Fatigue in Multiple Sclerosis*. Washington, DC: Paralyzed Veterans of America

Faulkner JR, Herrmann JE, Wood MJ *et al* 2004 Reactive astrocytes protect tissue and preserve function after spinal cord injury. *J Neurosci* **24**: 2143–2155

Favorova OO, Andreewski TV, Boiko AN *et al* 2002 The chemokine receptor CCR5 deletion mutation is associated with MS in HLA-DR4-positive Russians. *Neurology* **59**: 1652–1655

Fawcett J, Skegg DCG 1988 Geographic distribution of MS in New Zealand. *Neurology* **38**: 416–418

Fawcett JW, Asher RA 1999 The glial scar and central nervous system repair. *Brain Res Bull* **49**: 377–391

Fazekas F, Offenbacher H, Fuchs S *et al* 1988 Criteria for an increased specificity of MRI interpretation in elderly subjects with suspected multiple sclerosis. *Neurology* **38**: 1822–1825

Fazekas F, Deisenhammer F, Strasser-Fuchs S *et al* and the Austrian Immunoglobulin in Multiple Sclerosis Study Group 1997 Randomised placebo-controlled trial of monthly intravenous immunoglobulin therapy in relapsing–remitting multiple sclerosis. *Lancet* **349**: 589–593

Fazekas F, Barkhof F, Filippi M *et al* 1999 The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. *Neurology* **53**: 448–456

Fazekas F, Strasser Fuchs S, Schmidt H *et al* 2000 Apolipoprotein E genotype related differences in brain lesions of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **69**: 25–28

Fazekas F, Strasser-Fuchs S, Kollegger H *et al* 2001 Apolipoprotein E epsilon 4 is associated with rapid progression of multiple sclerosis. *Neurology* **57**: 853–857

Fazzone HE, Lefton DR, Kupersmith MJ 2003 Optic neuritis: correlation of pain and magnetic resonance imaging. *Ophthalmology* **110**: 1646–1649

Feakes R, Chataway J, Sawcer S *et al* 1998 Susceptibility to multiple sclerosis and the immunoglobulin heavy chain gene cluster. *Ann Neurol* **44**: 984

Feakes R, Sawcer S, Chataway J *et al* 1999 Exploring the dense mapping of a region of potential linkage in complex disease: an example in multiple sclerosis. *Genet Epidemiol* **17**: 51–63

Feakes R, Sawcer S, Broadley S *et al* 2000a Interleukin 1 receptor antagonist (IL-1ra) in multiple sclerosis. *J Neuroimmunol* **105**: 96–101

Feakes R, Sawcer S, Smillie B *et al* 2000b No evidence for the involvement of interleukin-2 or the immunoglobulin heavy chain cluster in determining genetic susceptibility to multiple sclerosis. *J Neurol Neurosurg Psych* **68**: 679

Fedetz M, Matezanz F, Pascual M *et al* 2001 The –174/-597 promoter polymorphisms in the interleukin-6 gene are not associated with susceptibility to multiple sclerosis. *J Neurol Sci* **190**: 69–72

Fedetz M, Alcina A, Fernandez O *et al* 2002 Analysis of –631 and -475 interleukin-2 promoter single nucleotide polymorphisms in multiple sclerosis. *Eur J Immunogenet* **29**: 389–390

Feigenson JS, Scheinberg L, Catalano M *et al* 1981 The cost-effectiveness of multiple sclerosis rehabilitation: a model. *Neurology* **31**: 1316–1322

Feigin I, Ogata J 1971 Schwann cells and peripheral myelin within human central nervous tissues: the mesenchymal character of Schwann cells. *J Neuropathol Exp Neurol* **30**: 603–612

Feigin I, Popoff N 1966 Regeneration of myelin in multiple sclerosis. *Neurology* **16**: 364–372

Feinstein A 2002 An examination of suicidal intent in patients with multiple sclerosis. *Neurology* **59**: 674–678

Feinstein A, Ron MA 1990 Psychosis associated with demonstrable brain disease. *Psych Med* **20**: 793–803

Feinstein A, Youl B, Ron M 1992a Acute optic neuritis: a cognitive and magnetic resonance imaging study. *Brain* **115**: 1403–1415

Feinstein A, Kartsounis LD, Miller DH *et al* 1992b Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. *J Neurol Neurosurg Psychiatry* **55**: 869–876

Feinstein A, Ron M, Thompson A 1993a A serial study of psychometric and magnetic resonance imaging changes in multiple sclerosis. *Brain* **116**: 569–602

Feinstein A, du Boulay G, Ron MA 1993b Psychotic illness in multiple sclerosis: a clinical and MRI study. *Br J Psychiatry* **161**: 680–685

Feinstein A, O'Connor P, Gray T, Feinstein K 1999 Pathological laughing and crying in multiple sclerosis: a preliminary report suggesting a role for the prefrontal cortex. *Mult Scler* **5**: 69–73

Feinstein A, Levine B, Protzner A 2000 Confabulation and multiple sclerosis: a rare association. *Mult Scler* **6**: 186–191

Feldman RG, Kelly-Hayes M, Conomy JP, Foley JM 1978 Baclofen for spasticity in multiple

sclerosis: double-blind crossover and three year study. *Neurology* **28**: 1094–1098
Felgenhauer K 1971 *Vergleichende Disc-elektrophorese von Serum un Liquor cerebrospinalis*, Stuttgart: Thieme
Felgenhauer K 1974 Protein size and cerebrospinal fluid composition. *Klin Wochenschr* **52**: 1158–1164
Felgenhauer K 1990 Psychiatric disorders in the encephalitic form of multiple sclerosis. *J Neurol* **237**: 11–18
Felts PA, Smith KJ 1992 Conduction properties of central nerve fibres remyelinated by Schwann cells. *Brain Res* **574**: 178–192
Felts PA, Smith KJ 1993 Segmental demyelinated central axons: the morphology of conducting axons. *Neuropathol Appl Neurobiol* **19**: 449–450
Felts PA, Smith KJ 1994 The use of potassium channel blocking agents in the therapy of demyelinating diseases. *Ann Neurol* **36**: 454
Felts PA, Kapoor R, Smith KJ 1995 A mechanism for ectopic firing in central demyelinated axons. *Brain* **118**: 1225–1231
Felts PA, Baker TA, Smith KJ 1997 Conduction in segmentally demyelinated mammalian central axons. *J Neurosci* **17**: 7267–7277
Felts PA, Deerinck TJ, Ellisman MH *et al* 1998 Sodium and potassium channel immunolocalisation in demyelinated and remyelinated central axons. *Neuropathol Appl Neurobiol* **24**: 154–155
Fenichel GM 1982 Neurological complications of immunisation. *Ann Neurol* **12**: 119–128
Fenichel GM 1999 Assessment: Neurologic risk of immunization. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **52**: 1546–1552
Fenyk-Melody JE, Garrison AE, Brunnert SR *et al* 1998 Experimental autoimmune encephalomyelitis is exacerbated in mice lacking the NOS2 gene. *J Immunol* **160**: 2940–2946
Ferguson B, Matyszak MK, Esiri MM, Perry VH 1997 Axonal damage in acute multiple sclerosis lesions. *Brain* **120**: 393–399
Ferguson FR, Liversedge LA 1959 A clinical aphorism in the diagnosis of multiple sclerosis. *Lancet* **i**: 1159–1160
Ferini-Strambi L, Filippi M, Martinelli V *et al* 1994 Nocturnal sleep study in multiple sclerosis: correlations with clinical and brain magnetic resonance imaging findings. *J Neurol Sci* **125**: 194–197
Fernandes-Filho F, Vedeler CA, Myhr KM *et al* 2002 TNF-alpha and -beta gene polymorphisms in multiple sclerosis: a highly significant role for determinants in the first intron of the TNF-beta gene. *Autoimmunity* **35**: 377–380
Fernandez O, Bufill E 1994 Prevalence of multiple sclerosis in Spain: validation of an epidemiological protocol in two geographically separated areas. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update.* Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 184–189
Fernandez O, Luque G, San Roman C *et al* 1994 The prevalence of multiple sclerosis in the Sanitary district of Velez-Malaga, southern Spain. *Neurology* **44**: 425–429
Fernandez O, Fernandez V, Alonso A *et al* 2004 DQB1*0602 allele shows a strong association with multiple sclerosis in patients in Malaga, Spain. *J Neurol* **251**: 440–444
Fernandez PA, Tang DG, Cheng L *et al* 2000 Evidence that axon-derived neuregulin promotes oligodendrocyte survival in the developing rat optic nerve. *Neuron* **28**: 81–90
Fernandez-Arquero M, Arroyo R, Rubio A *et al* 1999 Primary association of a TNF gene polymorphism with susceptibility to multiple sclerosis. *Neurology* **53**: 1361–1363
Fernando KTM, McLean MA, Chard DT *et al* 2004 Elevated white matter myo-inositol in clinically isolated syndromes suggestive of multiple sclerosis. *Brain* **127**:1361–1369
Ferrari MD, Hilkens PHE, Kremer B *et al* 1988 Intermittent pyramidal claudication as presenting and sole symptom in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **51**: 147–148
Ferri C, Sciacca FL, Veglia F *et al* 1999 APOEε2–4 and –491 polymorphisms are not associated with MS. *Neurology* **53**: 888–889
Ferri C, Sciacca FL, Grimaldi L *et al* 2000 Lack of association between IL-1A and IL-1B promoter polymorphisms and multiple sclerosis. *J Neurol Neurosurg Psychiatry* **69**: 564–5
Ferriby D, De Sèze J, Stojkovic T *et al* 2001 Long-term follow-up of neurosarcoidosis. *Neurology* **57**: 927–929
Fewster ME, Kies B 1984 HLA antigens in multiple sclerosis in coloured South Africans. *J Neurol Sci* **66**: 175–181
Feys P, Helsen W, Liu X *et al* 2005 Effects of peripheral cooling on intention tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **76**: 373–379
ffrench Constant C, Raff MC 1986 Proliferating bipotential glial progenitor cells in adult rat optic nerve. *Nature* **319**: 499–502
Fiebich BL, Lieb K, Engels S, Heinrich M 2002 Inhibition of LPS-induced p42/44 MAP kinase activation and iNOS/NO synthesis by parthenolide in rat primary microglial cells. *J Neuroimmunol* **132**: 18–24
Field EJ 1979 Multiple sclerosis: recent advances in aethiopathogenesis. In: Smith WT, Cavanagh JB (eds) *Recent Advances in Neuropathology I*. London: Churchill Livingstone, pp. 277–298
Field EJ 1989 *Multiple Sclerosis. A Conceptual Reappraisal with Heuristic Implications*. Springfield, IL: C.C. Thomas
Fielder AHL, Batchelor JR, Vakarelis BN, Compston DAS, McDonald WI 1981 Optic neuritis and multiple sclerosis: do factor B alleles influence progression of disease? *Lancet* **ii**: 1246–1248
Fiette L, Aubert C, Brahic M, Rossi CP 1993 Theiler's virus infection of b2-microglobulin deficient mice. *J Virol* **67**: 589–592
Fife BT, Huffnagle GB, Kuziel WA, Karpus WJ 2000 CC chemokine receptor 2 is critical for induction of experimental autoimmune encephalomyelitis. *J Exp Med* **192**: 899–906
Fife C, Otto G, Capsuto EG *et al* 2001 Incidence of pressure ulcers in a neurologic intensive care unit. *Crit Care Med* **29**: 283–290
Filipovic R, Jakovcevski I, Zecevic N 2003 GRO-alpha and CXCR2 in the human fetal brain and multiple sclerosis lesions. *Dev Neurosci* **25**: 279–290
Filipovic SR, Drulovic J, Stojsavljevic N, Levic Z 1997 The effects of high-dose intravenous methylprednisolone on event-related potentials in patients with multiple sclerosis. *J Neurol Sci* **152**: 147–153
Filippi M, Horsfield MA, Morrissey SP *et al* 1994 Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. *Neurology* **44**: 635–641
Filippi M, Paty DW, Kappos L *et al* 1995a Correlations between changes in disability and T_2-weighted brain MRI activity in multiple sclerosis: a follow-up study. *Neurology* **45**: 255–260
Filippi M, Campi A, Martinelli V *et al* 1995b Comparison of triple dose versus standard dose gadolinium-DTPA for detection of MRI enhancing lesions in patients with primary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* **59**: 540–544
Filippi M, Horsfield MA, Tofts PS *et al* 1995c Quantitative assessment of MRI lesion load in monitoring the evolution of multiple sclerosis. *Brain* **118**: 1601–1612
Filippi M, Campi A, Martinelli V *et al* 1995d A brain MRI study of different types of chronic-progressive multiple sclerosis. *Acta Neurol Scand* **91**: 231–233
Filippi M, Campi A, Martinelli V *et al* 1995e Transitional progressive multiple sclerosis: MRI and MTI findings. *Acta Neurol Scand* **92**: 178–182
Filippi M, Yousry T, Baratti C *et al* 1996 Quantitative assessment of MRI lesion load in multiple sclerosis. A comparison of conventional spin echo with fast fluid-attenuated inversion recovery. *Brain* **119**: 1349–1355
Filippi M, Horsfield MA, Ader HJ *et al* 1998a Guidelines for using quantitative measures of brain magnetic resonance imaging abnormalities in monitoring the treatment of multiple sclerosis. *Ann Neurol* **43**: 499–506
Filippi M, Rocca MA, Martino G, Horsfield MA, Comi G 1998b Magnetization transfer changes in the normal appearing white matter precede the appearance of enhancing lesions in patients with multiple sclerosis. *Ann Neurol* **43**: 809–814
Filippi M, Rocca MA, Rizzo G *et al* 1998c Magnetization transfer ratios in multiple sclerosis lesions enhancing after different doses of gadolinium. *Neurology* **50**: 1289–1293
Filippi M, Iannucci G, Tortorella C *et al* 1999a Comparison of MS clinical phenotypes

using conventional and magnetization transfer MRI. *Neurology* **52**: 588–594

Filippi M, Rocca MA, Moiola L *et al* 1999b MRI and magnetization transfer imaging changes in the brain and cervical cord of patients with Devic's neuromyelitis optica. *Neurology* **53**: 1705–1710

Filippi M, Rovaris M, Iannucci G *et al* 2000a Whole brain volume changes in patients with progressive MS treated with cladribine. *Neurology* **55**: 1714–1718

Filippi M, Rovaris M, Rice GP *et al* 2000b The effect of cladribine on T1 'black hole' changes in progressive MS. *J Neurol Sci* **176**: 42–44

Filippi M, Rovaris M, Rocca MA *et al* 2001a Glatiramer acetate reduces the proportion of new MS lesions evolving into 'black holes'. *Neurology* **57**: 731–733

Filippi M, Wolinsky JS, Sormani MP, Comi G for the European/Canadian Glatiramer Acetate Study Group 2001b Enhancement frequency decreases with increasing age in relapsing–remitting multiple sclerosis. *Neurology* **56**: 422–423

Filippi M, Rocca MA, Colombo B *et al* 2002a Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *Neuroimage* **15**: 559–567

Filippi M, Rocca MA, Falini A *et al* 2002b Correlations between structural CNS damage and functional MRI changes in primary progressive MS. *Neuroimage* **15**: 537–546

Filippi M, Sormani MP, Wolinsky J *et al* 2002c Glatiramer acetate reduces the proportion of new MS lesions evolving into 'black holes'. *Neurology* **58**: 1440–1441

Filippi M, Bozzali M, Rovaris M *et al* 2003 Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis. *Brain* **126**: 433–437

Filippi M, Rovaris M, Inglese M *et al* 2004a Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet* **364**: 1489–1496

Filippi M, Rocca MA, Mezzapesa DM *et al* 2004b Simple and complex movement-associated functional MRI changes in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis. *Hum Brain Mapping* **21**: 108–117

Filippini G, Munari L, Incorvaia B *et al* 2003a Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet* **361**: 545–552

Filippini G, Munari L, Ebers G *et al* 2003b Interferons in relapsing remitting multiple sclerosis (letter). *Lancet* **361**: 1823

Filippini G, Munari L, Ebers G *et al* 2003c Interferons in relapsing remitting multiple sclerosis (letter) *Lancet* **361**: 1824–1825

Fillmore PD, Brace M, Troutman SA *et al* 2003 Genetic analysis of the influence of neuroantigen-complete Freund's adjuvant emulsion structures on the sexual dimorphism and susceptibility to experimental allergic encephalomyelitis. *Am J Pathol* **163**: 1623–1632

Finelli PF 1991 Conjugal multiple sclerosis: a clinical and laboratory study. *Neurology* **41**: 1320–1321

Fink JK 2002 Hereditary spastic paraplegia: the pace quickens. *Ann Neurol* **51**: 669–672

Finkel MJ, Halperin JJ 1992 Nervous system Lyme borreliosis: revisited. *Arch Neurol* **49**: 102–107

Finkelman FD 1995 Relationships among antigen presentation, cytokines, immune deviation and autoimmune disease. *J Exp Med* **182**: 279–282

Finsen BR, Tönder N, Xavier GF *et al* 1993 Induction of microglial immunomolecules by anterogradely degenerating mossy fibers in the rat hippocampal formation. *J Chem Neuroanat* **6**: 276–275

Finsterer J, Grass R, Stollberger C, Mamoli B 1998 Immunoglobulins in acute, parainfectious, disseminated encephalomyelitis. *Clin Neuropharmacol* **21**: 258–261

Fiorentino DF, Bond MW, Mosmann TR 1989 Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. *J Exp Med* **170**: 2081–2095

Fiotti N, Zivadinov R, Altamura N *et al* 2004 MMP-9 microsatellite polymorphism and multiple sclerosis. *J Neuroimmunol* **152**: 147–153

Firnhaber W, Lauer K (eds) 1994 *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press

Firouzi R, Rolland A, Michel M *et al* 2003 Multiple sclerosis associated retrovirus particles cause T-lymphocyte-dependent death with brain hemorrhage in humanized SCID mice model. *J Neurovirol* **9**: 79–93

Firth D 1948 *The Case of Augustus D'Este*. Cambridge: Cambridge University Press

Fischer BH, Marks M, Reith T 1983 Hyperbaric oxygen treatment of multiple sclerosis: a randomised, placebo controlled double-blind study. *N Engl J Med* **308**: 181–186

Fischer C, Joyeux O, Haguenauer JP *et al* 1984 Surdité et acouphènes lors de poussées dans 10 cas de sclérose en plaques. *Rev Neurol* **140**: 117–125

Fischer D, He Z, Benowitz LI 2004 Counteracting the Nogo receptor enhances optic nerve regeneration if retinal ganglion cells are in an active growth state. *J Neurosci* **24**: 1646–1651

Fischer JS, LaRocca NG, Miller DM *et al* 1999 Recent developments in the assessment of quality of life in multiple sclerosis. *Mult Scler* **5**: 251–259

Fischer JS, Priore RL, Jacobs LD *et al* 2000 Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Ann Neurol* **48**: 885–892

Fisher A, Gresty M, Chambers B, Rudge P 1983 Primary position upbeating nystagmus. *Brain* **106**: 949–964

Fisher D, He Z, Benowitz Li 2004 Counteracting the Nogo receptor enhances optic nerve regeneration if retinal ganglion cells are in an active growth state. *J Neurosci* **24**: 1646–1651

Fisher E, Rudick RA, Cutter G *et al* 2000 Relationship between brain atrophy and disability: an 8-year follow-up study of multiple sclerosis patients. *Mult Scler* **6**: 373–377

Fisher E, Rudick RA, Simon JH *et al* 2002 Eight-year follow up study of brain atrophy in patients with MS. *Neurology* **59**: 1412–1420

Fisher M, Long RR, Drachman DA 1985 Hand muscle atrophy in multiple sclerosis. *Arch Neurol* **40**: 811–815

Fishman RA 1992 *Cerebrospinal Fluid in Diseases of the Nervous System*, Philadephia: W.B. Saunders

Fisk JD, Pontefract A, Ritvo PG *et al* 1994 The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* **21**: 9–14

Fiten P, Vandenbroeck K, Dubois B *et al* 1999 Microsatellite polymorphisms in the gene promotor of monocyte chemotactic protein-3 and analysis of the association between monocyte chemotactic protein-3 alleles and multiple sclerosis development. *J Neuroimmunol* **95**: 195–201

Flachenecker P, Wolf, A, Krauser M *et al* 1999 Cardiovascular autonomic dysfunction in multiple sclerosis: correlation with orthostatic intolerance. *J Neurol* **246**: 578–586

Flachenecker P, Reiners K, Krauser M *et al* 2001 Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. *Mult Scler* **7**: 327–334

Flashman JF, Latham O 1915 A contribution to the study of the aetiology of disseminated sclerosis. *Med J Aust* **2**: 265–269

Flensner G, Lindencrona C 2002 The cooling-suit: case studies of its influence on fatigue among eight individuals with multiple sclerosis. *J Adv Nurs* **37**: 541–550

Flechter S, Vardi J, Pollak L, Rabey JM 2002 Comparison of glatiramer acetate (Copaxone) and interferon beta-1b (Betaferon) in multiple sclerosis patients: an open-label 2-year follow-up. *J Neurol Sci* **197**: 51–55

Flügel A, Willem M, Berkowicz T, Wekerle H 1999 Gene transfer into $CD4^+$ T lymphocytes: green fluorescent protein engineered, encephalitogenic T cells used to illuminate immune responses in the brain. *Nature Med* **5**: 843–847

Flügel A, Schwaiger F-W, Neumann H *et al* 2000 Neuronal FasL induces cell death of encephalitogenic T lymphocytes. *Brain Pathol* **10**: 353–364

Flügel A, Berkowicz T, Ritter T *et al* 2001a Migratory activity and functional changes of green fluorescent effector T cells before and during experimental autoimmune encephalomyelitis. *Immunity* **14**: 547–560

Flügel A, Matsumoro K, Neumann H *et al* 2001b Anti inflammatory activity of nerve growth factor in experimental autoimmune encephalomyelitis: inhibition of monocyte

transendothelial migration. *Eur J Immunol* **31**: 11–22
Fog T 1950 Topographic distribution of plaques in the spinal cord in multiple sclerosis. *Arch Neurol* **63**: 382–414
Fog T 1951 ACTH behandling ved sclerosis disseminata. *Nordisk Medicin* **46**: 1742–1748
Fog T 1965 The topography of plaques in multiple sclerosis with special reference to cerebral plaques. *Acta Neurol Scand* **41 (Suppl 15)**: 1–161
Fog T 1966 The course of multiple sclerosis. *Acta Neurol Scand* **42**: 608–611
Fog T 1980 Interferon treatment of multiple sclerosis patients: a pilot study. In: Boese A (ed.) *Search for the Cause of Multiple Sclerosis and other Chronic Diseases of the Nervous System.* Weinheim: Verlag Chemie, pp. 491–493
Fog T, Hyllested K 1966 Prevalence of disseminated sclerosis in the Faroes, the Orkneys, and Shetland. *Acta Neurol Scand* **42 (Suppl 19)**: 9–11
Fog T, Linnemann F 1970 The course of multiple sclerosis in 73 cases with computer-designed curves. *Acta Neurol Scand* **46 (Suppl)**: 1–175
Fogarty M, Richardson WD, Kessaris N 2005 A subset of oligodendrocytes generated from radial glia in the dorsal spinal cord. *Development* **132**: 1951–1959
Fogdell A, Olerup O, Vrethem M, Hillert J 1997 Linkage analysis of HLA class II genes in Swedish multiplex families with multiple sclerosis. *Neurology* **48**: 758–762
Fogdell-Hahn A, Ligers A, Gronning M *et al* 2000 Multiple sclerosis: a modifying influence of HLA class I genes in an HLA class II associated autoimmune disease. *Tissue Antigens* **55**: 140–148
Foix C, Alajouanine T 1926 La myelité necrotique subaigue. *Rev Neurol* **2**: 1–42
Fok-Seang J, DiProspero NA, Meiners S *et al* 1998 Cytokine-induced changes in the ability of astrocytes to support migration of oligodendrocyte precursors and axon growth. *Eur J Neurosci* **10**: 2400–2415
Folgar S, Gatto EM, Raina G, Micheli F 2003 Parkinsonism as a manifestation of multiple sclerosis. *Mov Disord* **18**: 108–110
Fontaine B, Seilhean D, Tourbah A *et al* 1994 Dementia in two histologically confirmed cases of multiple sclerosis: one case with isolated dementia and one case associated with psychiatric symptoms. *J Neurol Neurosurg Psychiatry* **57**: 353–359
Fontaine B, Cournu I, Arnaud I *et al* 1999 Chromosome 17q22-q24 and multiple sclerosis genetic susceptibility. *Genes Immun* **1**: 149–150
Fontana A, Grieder A, Arrenbrecht ST, Grob P 1980 *In vitro* stimulation of glia cells by a lymphocyte produced factor. *J Neurol Sci* **46**: 55–62
Foong J, Ron MA 2003 Neuropsychiatry: cognition and mood disorders. In: McDonald WI, Noseworthy JH (eds) *Multiple Sclerosis*, 2nd edn. London: Butterworth Heinemann, pp. 115–124
Foong J, Rozewicz L, Quaghebeur G *et al* 1997 Executive function in multiple sclerosis: the role of frontal lobe pathology. *Brain* **120**: 15–26
Foong J, Davie CA, Thompson AJ *et al* 1999 Correlates of executive function in multiple sclerosis: use of MRS as an index of focal pathology. *J Neuropsychiatry Clin Neurosci* **11**: 45–50
Foong J, Rozewicz L, Chong WK *et al* 2000 A comparison of neuropsychological deficits in primary and secondary progressive multiple sclerosis. *J Neurol Sci* **247**: 97–101
Foote AK, Blakemore WF 2005 Inflammation stimulates remyelination in areas of chronic demyelination. *Brain* **128**: 528–539
Forbes RB, Swingler RJ 1999 Estimating the prevalence of multiple sclerosis in the United Kingdom by using capture–recapture methodology. *Am J Epidemiol* **149**: 1016–1024
Forbes RB, Wilson SV, Swingler RJ 1999 The prevalence of multiple sclerosis in Tayside, Scotland: do latitudinal gradients really exist? *J Neurol* **246**: 1033–1040
Ford AL, Foulcher E, Lemckert FA, Sedgwick JD 1996 Microglia induce CD4 T lymphocyte final effector function and death. *J Exp Med* **184**: 1737–1745
Ford B, Tampieri D, Francis G 1992 Long-term follow-up of acute partial transverse myelopathy. *Neurology* **42**: 250–252
Ford HL, Gerry E, Airey CM *et al* DR 1998a The prevalence of multiple sclerosis in the Leeds Health Authority. *J Neurol Neurosurg Psych* **64**: 605–610
Ford HL, Trigwell P, Johnson M 1998b The nature of fatigue in multiple sclerosis. *J Psychosom Res* **45**: 33–38
Ford HL, Tennant GE, Whalley A *et al* 2001 Developing a disease-specific quality of life measure for people with multiple sclerosis. *Clin Rehabil* **15**: 247–258
Ford HL, Gerry E, Johnson M, Williams R 2002 A prospective study of the incidence, prevalence and mortality of multiple sclerosis in Leeds. *J Neurol* **249**: 260–265
Ford ML, Onami TM, Sperling AI *et al* 2003 CD43 modulates severity and onset of experimental autoimmune encephalomyelitis. *J Immunol* **171**: 6527–6533
Forrester K, Ambs S, Lupold SE *et al* 1996 Nitric oxide-induced p53 accumulation and regulation of inducible nitric oxide synthase expression by wild-type p53. *Proc Natl Acad Sci USA* **93**: 2442–2447
Forsthuber T, Yip HC, Lehmann PV 1996 Induction of Th1 and Th2 immunity in neonatal mice. *Science* **271**: 1728–1730
Fossati G, Cooke A, Papafio RQ *et al* 1999 Triggering a second T cell receptor on diabetogenic T cells can prevent induction of diabetes. *J Exp Med* **190**: 577–583
Fossier P, Blanchard B, Ducrocq C *et al* 1999 Nitric oxide transforms serotonin into an inactive form and this affects neuro-modulation. *Neuroscience* **93**: 597–603
Foster RM, Harries JR 1970 Multiple sclerosis in the African. *Br Med J* **3**: 628
Fourrier A, Touzé E, Alpérovitch A, Bégaud B 1999 Association between hepatitis B vaccine and multiple sclerosis: a case-control study. *Pharmacoepidemiology and Drug Safety* **8 (Suppl)**: S140–S141
Fourrier A, Bégaud B, Alpérovitch A *et al* 2001 Hepatitis B vaccination and first episodes of central nervous system demyelinating disorders: a comparison between reported and expected number of cases. *Br J Clin Pharmacol* **51**: 489–490
Fowler CJ 1997 The cause and management of bladder, sexual and bowel symptoms in multiple sclerosis. *Baillières Clin Neurol* **6**: 447–466
Fowler CJ, van Kerrbroeck P, Nordenbo A, van Poppel H 1992a Treatment of lower urinary tract dysfunction in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **55**: 986–969
Fowler CJ, Jewkes D, McDonald WI, Lynn B, de Groat WC 1992b Intravesical capsaicin for neurogenic bladder dysfunction. *Lancet* **339**: 1239
Fowler CJ, Beck RO, Gerrard S, Betts CD, Fowler CG 1994 Intravesical capsaicin for treatment of detrusor hyperreflexia. *J Neurol Neurosurg Psychiatry* **57**: 169–173
Fowler CJ, Miller JR, Sharief M 1999 Viagra (sildenafil citrate) for the treatment of erectile dysfunction in men with multiple sclerosis. *Ann Neurol* **46**: 497
Fowler CJ, Miller JR, Sharief MK *et al* 2005 A double blind, randomised study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **76**: 700–705
Fox CM, Bensa S, Bray I, Zajicek JP 2004 The epidemiology of multiple sclerosis in Devon: a comparison of the new and old classification criteria. *J Neurol Neurosurg Psychiatry* **75**: 56–60
Fox NC, Jenkins R, Lary SM *et al* 2000 Progressive cerebral atrophy in MS: a serial study using registered, volumetric MRI. *Neurology* **54**: 807–812
Fraenkel M, Jakob A 1913 Zur Pathologie der multiplen Sklerose mit besonderer Berücksichtigung der akuten Formen. *Z Neurol Psychiatr* **14**: 565–603
Fraker PJ, Lill-Elghanian DA 2004 The many roles of apoptosis in immunity as modified by aging and nutritional status. *J Nutr Health Aging* **8**: 56–63
Francabandera F, Holland N, Wiesel-Levison P, Scheinberg L 1988 Multiple sclerosis rehabilitation: inpatient versus outpatient. *Rehab Nursing* **13**: 251–253
Franciotta DM, Grimaldi LM, Martino GV *et al* 1989 Tumor necrosis factor in serum and cerebrospinal fluid of patients with multiple sclerosis. *Ann Neurol* **26**, 787–789
Franciotta D, Dondi E, Bergamaschi R *et al* 1995 HLA complement gene polymorphisms in multiple sclerosis: a study on 80 Italian patients. *J Neurol* **242**: 64–68
Franciotta D, Bergamashi R, Piccolo G *et al* 2000 Multiple secondary Leber's hereditary optic neuropathy mutations in Italian

patients with multiple sclerosis. *J Neurol* **247**: 304–305
Franciotta D, Martino G, Zardini E *et al* 2001 Serum and CSF levels of MCP-1 and IP-10 in multiple sclerosis patients with acute and stable disease and undergoing immunomodulatory therapies. *J Neuroimmunol* **115**: 192–198
Francis DA, Heron JR 1985 Ocular flutter in suspected multiple sclerosis: a presenting paroxysmal manifestation. *Postgrad Med J* **61**: 333–334
Francis DA, Brazier DM, Batchelor JR *et al* 1986 GM allotypes in multiple sclerosis influence susceptibility in HLA DQ1 positive patients from the north east of Scotland. *Clin Immunol Immunopathol* **41**: 409–416
Francis DA, Batchelor JR, McDonald WI 1987a Multiple sclerosis in north east Scotland. An association with HLA DQw 1. *Brain* **110**: 181–196
Francis DA, Compston DAS, Batchelor JR, McDonald WI 1987b A reassessment of the risk of multiple sclerosis developing in patients with optic neuritis after extended follow-up. *J Neurol Neurosurg Psychiatry* **50**: 758–765
Francis DA, Bain P, Swan AV, Hughes RAC 1991a An assessment of disability rating scales used in multiple sclerosis. *Arch Neurol* **48**: 299–301
Francis DA, Thompson AJ, Brookes P *et al* 1991b Multiple sclerosis and HLA: is the susceptibility gene really HLA-DR or -DQ? *Hum Immunol* **32**: 119–124
Francis GS, Freedman MS, Antel JP 1997 Failure of intravenous immunoglobulin to arrest progression of multiple sclerosis: a clinical and MRI based study. *Mult Scler* **3**: 370–376
Francis GS, Rice GP, Alsop JC 2005 Interferon beta-1a in MS: results following development of neutralizing antibodies in PRISMS. *Neurology* **65**: 48–55
Frank JA, Miller BR, Arbab AS *et al* 2003 Clinically applicable labeling of mammalian and stem cells by combining superparamagnetic iron oxides and transfection agents. *Radiology* **228**: 480–487
Frank JA, Richert N, Bash C *et al* 2004 Interferon-β-1b slows progression of atrophy in RRMS: three-year follow-up in NAb– and NAb+ patients. *Neurology* **62**: 719–725
Frank MM, Basta M, Fries LF 1992 The effect of intravenous immune globulin on complement-dependent immune damage of cells and tissues. *Clin Immunol Immunopathol* **62**: S82–S86
Franklin GM, Nelson LM, Heaton RK *et al* 1988 Stress and its relationship to acute exacerbations in multiple sclerosis. *J Neuol Rehab* **2**: 7–11
Franklin GM, Nelson LM, Filley CM, Heaton RK 1989 Cognitive loss in multiple sclerosis: case reports and review of literature. *Arch Neurol* **46**: 162–167
Franklin RJ 2002 Why does remyelination fail in multiple sclerosis? *Nat Rev Neurosci* **3**: 705–714
Franklin RJ, Bayley SA, Blakemore WF 1996 Transplanted CG-4 cells (an oligodendrocyte progenitor cell line) survive, migrate and contribute to repair of areas of demyelination in X-irradiated and damaged spinal cord but not in normal spinal cord. *Exp Neurol* **137**: 263–276
Frasson E, Polo A, di Summa A *et al* 1997 Multiple sclerosis associated with duplicated CMT1A: a report of two cases. *J Neurol Neurosurg Psychiatry* **63**: 413–414
Freal JE, Kraft GH, Coryell JK 1984 Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehab* **65**: 135–138
Frederick TJ, Wood TL 2004 IGF-I and FGF-2 coordinately enhance cyclin D1 and cyclin E-cdk2 association and activity to promote G1 progression in oligodendrocyte progenitor cells. *Mol Cell Neurosci* **25**: 480–492
Frederiksen JL 1999 *A Prospective Study of Acute Optic Neuritis: Clinical, MRI, CSF, Neurophysiological and HLA Findings*. Copenhagen: FADL Publishers, p. 83
Frederiksen JL, Larsson HBW, Ottovay E *et al* 1991a Acute optic neuritis with normal visual acuity. *Acta Ophthalmol* **69**: 357–366
Frederiksen JL, Larsson HBW, Olesen J, Stigsby B 1991b MRI, VEP, SEP and biothesiometry suggest monosymptomatic acute optic neuritis to be a first manifestation of multiple sclerosis. *Acta Neurol Scand* **83**: 343–350
Fredrikson S 1996 Nasal spray desmopressin treatment of bladder dysfunction in patients with multiple sclerosis. *Acta Neurol Scand* **94**: 31–34
Fredrikson S, Kam-Hansen S 1989 The 150-year anniversary of multiple sclerosis: does its early history give an etiological clue? *Perspect Biol Med* **32**: 237–243
Fredrikson S, Eneroth P, Link H 1987 Intrathecal production of neopterin in aseptic meningo-encephalitis and multiple sclerosis. *Clin Exp Immunol* **67**: 76–81
Fredrikson S, Michelsberg J, Hillert J *et al* 1992 Conjugal multiple sclerosis: immunogenetic characterisation and analysis of T- and B-cell reactivity to myelin antigens. *Neurology* **42**: 577–582
Fredrikson S, Cheng Q, Jiang GX, Wasserman D 2003 Elevated suicide risk among patients with multiple sclerosis in Sweden. *Neuroepidemiology* **22**: 146–152
Freeborough PA, Fox NC 1997 The boundary shift integral: an accurate and robust measure of cerebral volume changes from registered repeat MRI. *IEEE Trans Med Imag* **16**: 623–629
Freeborough PA, Fox NC 1998 Modeling brain deformations in Alzheimer disease by fluid registration of serial 3D MR images. *J Comput Assist Tomogr* **22**: 838–843
Freedman DM, Dosemeci M, Alavanja MC 2000 Mortality from multiple sclerosis and exposure to residential and occupational solar radiation: a case-control study based on death certificates. *Occup Environ Med* **57**: 418–421
Freedman MS, Atkins HL 2004 Suppressing immunity in advancing MS. Too much too late, or too late for much? *Neurology* **62**: 168–169
Freedman MS, Gray TA 1989 Vascular headache: a presenting symptom of multiple sclerosis. *Can J Neurol Sci* **16**: 63–66
Freedman MS, Ruijs TCG, Selin LK, Antel JP 1991 Peripheral blood γδ T cells lyse fresh human brain-derived oligodendrocytes. *Ann Neurol* **30**: 794–800
Freedman MS, King J, Oger J *et al* 2003 Interferons in relapsing remitting multiple sclerosis. *Lancet* **361**: 1822–1823; author reply 1823–1824
Freedman MS, Murzeniok P, Wang W *et al* 2004 Human gamma-delta T cells block conduction in a novel xenogeneic *in vitro* model for studying CNS-immune interactions. *J Neuroimmunol* [abstracts]
Freedman MS, Thompson EJ, Deisenhammer F *et al* 2005a Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis. A consensus statement. *Arch Neurol* **62**: 865–870
Freedman MS, Francis GS, Sanders EA *et al* 2005b Randomized study of once-weekly interferon beta-1la therapy in relapsing multiple sclerosis: three-year data from the OWIMS study. *Mult Scler* **11**: 41–45
Freeman JA, Thompson A 2000 Community services in multiple sclerosis: still a matter of chance. *J Neurol Neurosurg Psychiatry* **69**: 728–732
Freeman JA, Thompson AJ 2003 Rehabilitation in multiple sclerosis. In: McDonald WI, Noseworthy JH (eds) *Multiple Sclerosis, 2nd edn,* Philadelphia: Butterworth-Heinemann, pp. 317–328
Freeman JA, Langdon DW, Hobart JC, Thompson AJ 1997 The impact of inpatient rehabilitation on progressive multiple sclerosis. *Ann Neurol* **42**: 236–244
Freeman JA, Langdon DW, Hobart JC, Thompson AJ 1999 Inpatient rehabilitation in multiple sclerosis: do the benefits carry over into the community? *Neurology* **52**: 50–56
Frei K, Siepl C, Groscurth P *et al* 1987 Antigen presentation and tumor cytotoxicity by interferon-gamma-treated microglial cells. *Eur J Immunol* **17**: 1271–1278
French Research Group on Multiple Sclerosis 1992 Multiple sclerosis in 54 twinships: concordance rate is independent of zygosity. *Ann Neurol* **32**: 724–727
Frerichs FT 1849 Ueber Hirnsklerose. *Arch Gesammte Med* **10**: 334–350
Frese A, Bethke F, Ludemann P, Stogbauer F 1999 Enhanced spasticity in primary progressive MS patients treated with interferon beta-1b. *Neurology* **53**: 1892–1893
Fridkis-Hareli M, Strominger JL 1998 Promiscuous binding of synthetic copolymer 1 to purified HLA-DR molecules. *J Immunol* **160**: 4386–4397
Fridkis-Hareli M, Teitelbaum D, Gurevich E *et al* 1994 Direct binding of myelin basic protein and synthetic copolymer 1 to class II major histocompatibility complex molecules on living antigen-presenting cells

– specificity and promiscuity. *Proc Natl Acad Sci USA* **91**: 4872–4876
Friede RL 1961 Enzyme histochemical studies in multiple sclerosis. *Arch Neurol* **5**: 433–443
Friedlander AH, Zeff S 1974 Atypical trigeminal neuralgia in patients with multiple sclerosis. *J Oral Surg* **32**: 301–303
Friedman GD 1987 *Primer of Epidemiology*. New York: McGraw-Hill International
Friedman JE, Lyons MJ, Cu G *et al* 1999 The association of the human herpesvirus-6 and MS. *Mult Scler* **5**: 355–362
Friedman JE, Zabriskie JB, Plank C *et al* 2005 A randomized clinical trial of valacyclovir in multiple sclerosis. *Mult Scler* **11**: 286–295
Friese MA, Fugger L 2005 Autoreactive $CD8^+$ T cells in multiple sclerosis: a new target for therapy? *Brain* **128**: 1747–1763
Frisén L, Hoyt WF 1974 Insidious atrophy and retinal nerve fibres in multiple sclerosis: fundoscopic identification in patients with and without visual complaint. *Arch Ophthalmol* **92**: 91–97
Frisén L, Hoyt WF, Bird AC, Weale RA 1973 Diagnostic uses of the Pulfrich phenomenon. *Lancet* **ii**: 385–386
Frith JA 1988 History of multiple sclerosis: an Australian persepctive. *Clin Exp Neurol* **25**: 7–16
Frith JA, McLeod JG 1988 Pregnancy and multiple sclerosis. *J Neurol Neurosurg Psychiatry* **51**: 495–498
Frith JA, McLeod JG, Basten A *et al* 1986 Transfer factor as a therapy for multiple sclerosis: a follow-up study. *Clin Exp Neurol* **22**: 149
Frith JA, McLeod JG, Hely M 2000 Acute optic neuritis in Australia: a 13 year prospective study. *J Neurol Neurosurg Psychiatry* **68**: 246
Fritz RB, Zhao ML 2001 Regulation of experimental autoimmune encephalomyelitis in the C57BL/6J mouse by NK1.1, DX5+, ab+ T cells. *J Immunol* **166**: 4209–4215
Fritz RB, Russell JP, Zhao M-L 1998 Persistence of an encephalitogenic T cell clone in the spinal cord during chronic, relapsing experimental autoimmune encephalomyelitis. *J Neuroimmunol* **89**: 1–9
Frohman EM, Frohman TC 2003 Horizontal monocular saccadic failure: an unusual clinically isolated syndrome progressing to multiple sclerosis. *Mult Scler* **9**: 55–58
Frohman EM, Zhang H, Dewey RB *et al* 2000 Vertigo in MS: utility of positional and particle repositioning maneuvers. *Neurology* **55**: 1566–1569
Frohman EM, Frohman TC, Fleckenstein J *et al* 2001 Ocular contrapulsion in multiple sclerosis: clinical features and pathophysiological mechanisms. *J Neurol Neurosurg Psychiatry* **70**: 688–692
Frohman EM, Frohman TC, Moreault AM 2002 Acquired sexual paraphilia in patient with multiple sclerosis. *Arch Neurol* **59**: 1006–1010
Frohman EM, Goodin DS, Calabresi PA *et al* 2003 The utility of MRI in suspected MS. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **61**: 602–611
Frohman EM, Dewey RB, Frohman TC 2004 An unusual variant of the dorsal midbrain syndrome in MS: clinical characteristics and pathophysiologic mechanisms. *Mult Scler* **10**: 322–325
Frohman EM, Frohman TC, Zee DS *et al* 2005 The neuro-ophthalmology of multiple sclerosis. *Lancet Neurol* **4**: 111–121
Frohman LP, Giurgis M, Turbin RE, Bielory L 2003 Sarcoidosis of the anterior visual pathways: 24 new cases. *J Neuroophthalmol* **23**: 190–197
Fromann C 1864 *Untersuchungen über die normale und pathologische Amatomie des Ruckenmarks, zweiter Theil*. Jena: Fromann
Fromann C 1878 *Untersuchungen über die Gewebsveränderungen bei der multiplen Sklerose des Gehirns und Rückenmarks*. Jena: Fromann
Frost EE, Buttery PC, Milner R, ffrench-Constant C 1999 Integrins mediate a neuronal survival signal for oligodendrocytes. *Curr Biol* **9**: 1251–1254
Frost EE, Nielsen JA, Le TQ, Armstrong RC 2003 PDGF and FGF2 regulate oligodendrocyte progenitor responses to demyelination. *J Neurobiol* **54**: 457–472
Früh K, Yang Y 1999 Antigen presentation by MHC class I and its regulation by interferon-γ. *Curr Opin Immunol* **11**: 76–81
Fruttiger M, Karlsson L, Hall AC *et al* 1999 Defective oligodendrocyte development and severe hypomyelination in PDGF-A knockout mice. *Development* **126**: 457–467
Frzovic D, Morris ME, Vowels L 2000 Clinical tests of standing balance: performance of persons with multiple sclerosis. *Arch Phys Med Rehab* **81**: 215–221
Fu L, Matthews PM, DeStefano N *et al* 1998 Imaging axonal damage of normal-appearing white matter in multiple sclerosis. *Brain* **121**: 103–113
Fugger L, Ryder LP, Morling N *et al* 1990a DNA typing for HAL-DPB1.02 and -DPB1.04 in multiple sclerosis and juvenile rheumatoid arthritis. *Immunogenetics* **32**: 150–156
Fugger L, Sandberg-Wollheim M, Morling N *et al* 1990b The germline repertoire of T-cell receptor beta chain genes in patients with relapsing remitting multiple sclerosis or optic neuritis. *Immunogenetics* **31**: 278–280
Fuhr P, Borggrefe-Chappuis A, Schindler C, Kappos L 2001 Visual and motor evoked potentials in the course of multiple sclerosis. *Brain* **124**: 2162–2168
Fujimoto S, Kondoh H, YamamotoY *et al* 1990 Holter electrocardiogram monitoring in nephrotic patients during methylprednisolone pulse therapy. *Am J Nephrol* **10**: 231–236
Fujinami RS, Oldstone MBA 1985 Amino acid homology between the encephalitogenic site of myelin basic protein (MBP) and virus: mechanism for autoimmunity. *Science* **230**: 1043–1046
Fukazawa T, Moriwaka F, Sugiyama K *et al* 1993 Cerebrospinal fluid IgG profiles and multiple sclerosis in Japan. *Acta Neurol Scand* **88**: 178–183
Fukazawa T, Moriwaka F, Hamada K *et al* 1997a Facial palsy in multiple sclerosis. *J Neurol* **244**: 483–488
Fukazawa T, Sasaki H, Kikuchi S, Hamada K, Hamada T, Tashiro K 1997b Dominantly inherited leukodystrophy showing cerebellar deficits, and spastic paraparesis: a new entity? *J Neurol* **244**: 446–449
Fukazawa T, Yanagawa T, Kikuchi S *et al* 1999a CTLA-4 gene polymorphism may modulate disease in Japanese multiple sclerosis patients. *J Neurol Sci* **171**: 49–55
Fukazawa T, Yabe I, Kikuchi S *et al* 1999b Association of vitamin D receptor gene polymorphism with multiple sclerosis in Japanese. *J Neurol Sci* **166**: 47–52
Fukazawa T, Kikuchi S, Sasaki H *et al* 2000a Genomic HLA profiles of MS in Hoikkaido, Japan: important role of DPB1*0501 allele. *J Neurol* **247**: 175–178
Fukazawa T, Yamasaki K, Ito H *et al* 2000b Both the HLA-DPB1 and -DRB1 alleles correlate with risk for multiple sclerosis in Japanese: clinical phenotypes and gender as important factors. *Tissue Antigens* **55**: 199–205
Fukazawa T, Kikuchi S, Niino M *et al* 2003 Multiphasic demyelinating disorder with acute transverse myelitis in Japanese. *J Neurol* **250**: 624–626
Fukazawa T, Kikuchi S, Miyagishi R *et al* 2005 CTLA-4 gene polymorphism is not associated with conventional multiple sclerosis in Japanese. *J Neuroimmunol* **159**: 225–229
Fukushima T, Mayanagi Y 1975 Neurophysiological examination (SEP) for the objective diagnosis of spinal lesions. In: Klug W, Brock M, Klinger M, Spoerri O (eds) *Adv Neurosurg* **2**: 158–168
Fulford KWM, Caterall RD, Delhanty JJ, Doniach D, Kremer M 1972 A collagen disorder of the nervous system presenting as multiple sclerosis. *Brain* **95**: 373–386
Fulton BP, Burne JF, Raff MC 1992 Visualisation of O-2A progenitor cells in developing and adult rat optic nerve by quisqualate-stimulated cobalt uptake. *J Neurosci* **12**: 4816–4833
Fulton JC, Grossman RI, Mannon LJ *et al* 1999 Familial multiple sclerosis: volumetric assessment in clinically symptomatic and asymptomatic individuals. *Mult Scler* **5**: 74–77
Funakawa I, Terao A 1998 Intractable hiccups and syncope in multiple sclerosis. *Acta Neurol Scand* **98**: 136–139
Funakawa I, Hara K, Yasuda T, Terao A 1993 Intractable hiccups and sleep apnea syndrome in multiple sclerosis: report of two cases. *Acta Neurol Scand* **88**: 401–405
Furlan R, Martino G, Galbiati F *et al* 1999 Caspase-1 regulates the inflammatory process leading to autoimmune demyelination. *J Immunol* **163**: 2403–2409

Furlan R, Brambilla E, Ruffini F *et al* 2001 Intrathecal delivery of IFN-gamma protects C57BL/6 mice from chronic-progressive experimental autoimmune encephalomyelitis by increasing apoptosis of central nervous system-infiltrating lymphocytes. *J Immunol* **167**: 1821–1829

Furtado GD, Olivares-Villagomez D, de Lafaille MAC *et al* 2001 Regulatory T cells in spontaneous autoimmune encephalomyelitis. *Immunol Rev* **182**: 122–134

Furukawa K, Barger SW, Blalock EM, Mattson MP 1996 Activation of K+ channels and suppression of neuronal activity by secreted beta-amyloid-precursor protein. *Nature* **379**: 74–78

Fux CA, Pfister S, Nohl F, Zimmerli S 2003 Cytomegalovirus-associated acute transverse myelitis in immunocompetent adults. *Clin Microbiol Infect* **9**: 1187–1190

Gabay L, Lowell S, Rubin LL, Anderson DJ 2003 Deregulation of dorsoventral patterning by FGF confers trilineage differentiation capacity on CNS stem cells in vitro. *Neuron* **40**: 485–499

Gabriel SB, Schaffner SF, Nguyen H *et al* 2002 The structure of haplotype blocks in the human genome. *Science* **296**: 2225–2229

Gade-Andavolu R, MacMurray JP, Blake H *et al* 1998 Association between the gamma-aminobutyric acid A3 receptor gene and multiple sclerosis. *Arch Neurol* **55**: 513–516

Gade-Andavolu R, Comings DE, MacMurray J *et al* 2004 RANTES: a genetic risk marker for multiple sclerosis. *Mult Scler* **10**: 536–539

Gaertner S, De Graaf KL, Greve B, Weissert R 2004 Antibodies against glycosylated native MOG are elevated in patients with multiple sclerosis. *Neurology* **63**: 2381–2383

Gaines AR, Varricchio F 1998 Interferon beta-1b injection site reactions and necroses. *Mult Scler* **4**: 70–73

Gaiser CN, Johnson MJ, de Lange G *et al* 1987 Susceptibility to multiple sclerosis associated with an immunoglobulin gamma 3 restriction length polymorphism. *J Clin Invest* **79**: 309–313

Galer BS, Lipton RB, Weinstein S *et al* 1990 Apoplectic headache and oculomotor nerve palsy: an unusual presentation of multiple sclerosis. *Neurology* **40**: 1465–1466

Galetta S, Schatz NJ, Glaser JS 1989 Acute sarcoid optic neuropathy with spontaneous recovery. *J Clin Neuroophthalmol* **9**: 27–32

Gall JC, Hayles AB, Siekert RG, Keith HM 1958 Multiple sclerosis in children. *Pediatrics* **21**: 703–709

Gallo A, Rovaris M, Riva R *et al* 2005 Diffusion-tensor magnetic resonance imaging detects normal appearing white matter damage unrelated to short-term disease activity in patients at the earliest clinical stage of multiple sclerosis. *Arch Neurol* **62**: 803–808

Gallo P, Piccinno M, Pagni S, Tavolato B 1988 Interleukin-2 levels in serum and cerebrospinal fluid of multiple sclerosis patients. *Ann Neurol* **24**: 795–797

Gallo P, Piccinno MG, Tavaloto B, Siden A 1991 A longitudinal study on IL-2, sIL-2R, IL-4 and IFN-gamma in multiple sclerosis CSF and serum. *J Neurol Sci* **101**: 227–232

Gallo P, Chiusole P, Sanzari M *et al* 1994 Effect of high dose steroid therapy on T cell subpopulations: a longitudinal study in MS patients. *Acta Neurol Scand* **89**: 95–101

Gallou M, Madigand M, Masse L *et al* 1983 Epidemiologie de la sclérose en plaques en Bretagne. *Presse Med* **12**: 995–999

Gambardella A, Valentino P, Labate A *et al* 2003 Temporal lobe epilepsy as a unique manifestation of multiple sclerosis. *Can J Neurol Sci* **30**: 228–232

GAMES and the Transatlantic Multiple Sclerosis genetics cooperative 2003 A meta-analysis of whole genome linkage screens in multiple sclerosis. *J Neuroimmunol* **143**: 39–46

GAMES Collaborative Group 2005 Linkage disequilibrium screening for multiple sclerosis implicates *JAG1* and *POU2AF1* as susceptibility genes in Europeans (submitted)

Gammon G, Klotz J, Ando D, Sercarz EE 1990 The T cell response to a multideterminant antigen: clonal heterogeneity of the T cell response, variation between syngeneic individuals and *in vitro* selection of T cell specificities. *J Immunol* **144**: 1571–1577

Gandevia SC, Allen GM, Butler JE, Taylor JL 1996 Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. *J Physiol* **490**: 529–536

Ganter P, Prince C, Esiri MM 1999 Spinal cord axonal loss in multiple sclerosis: a post-mortem study. *Neuropathol Appl Neurobiol* **25**: 459–467

Garbern JY, Yool DA, Moore GJ *et al* 2002 Patients lacking the major CNS myelin protein, proteolipid protein 1, develop length-dependent axonal degeneration in the absence of demyelination and inflammation. *Brain* **125**: 551–561

Garcia JR, Rodriguez S, Henriquez MS *et al* 1989 Prevalence of multiple sclerosis in Lanzarote (Canary Islands). *Neurology* **39**: 265–567

Garcin R 1936 Sclérose en plaques familiale et paraplegie spasmodique familiale a forme de sclérose en plaques. *Rev Neurol* **65**: 58–60

Garcin R, Godlewski S, Lapresle J 1960 Névralgie du trijumau et sclérose en plaques (à propos d'une observation anatomo-clinique). *Rev Neurol* **102**: 441–451

Garcin R, Lapresle J, Fardeau M 1962 Documents pour servir a l'étude des amyotrophies et des abolitions durable des réflexes tendineux observeés dans la sclérose en plaques. *Rev Neurol* **107**: 417–431

Gard AL, Pfeiffer SE 1990 Two proliferative stages of the oligodendrocyte lineage ($A2B5^+O4^-$ and $O4^+GalC^-$) under different mitogenic control. *Neuron* **5**: 615–625

Gardinier MV, Amiguet P, Linington C, Matthieu J-M 1992 Myelin/oligodendrocyte glycoprotein is a unique member of the immunoglobulin superfamily. *J Neurosci Res* **33**: 177–187

Garson JA, Tuke PW, Giraud P *et al* 1998 Detection of virion-associated MSRV-RNA in serum of patients with multiple sclerosis. *Lancet* **351**: 33

Garthwaite G, Goodwin DA, Garthwaite J 1999 Nitric oxide stimulates cGMP formation in rat optic nerve axons, providing a specific marker of axon viability. *Eur J Neurosci* **11**: 4367–4372

Garthwaite G, Goodwin DA, Batchelor AM *et al* 2002 Nitric oxide toxicity in CNS white matter: an in vitro study using rat optic nerve. *Neuroscience* **109**: 145–155

Gasperini C, Grasso MG, Fiorelli M *et al* 1995 A controlled study of potential risk factors preceding exacerbation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **59**: 303–305

Gasperini C, Pozzilli CD, Bastianelli S *et al* 1998 Effect of steroids on Gd-enhancing lesions before and during recombinant beta interferon 1α treatment in relapsing remitting multiple sclerosis. *Neurology* **50**: 403–406

Gasperini C, Paolillo A, Giugni E *et al* 2002 MRI brain volume changes in relapsing remitting multiple sclerosis patients treated with interferon beta-1a. *Mult Scler* **8**: 119–123

Gass A, Barker GJ, Kidd D *et al* 1994 Correlation of magnetisation transfer ratio with clinical disability in multiple sclerosis. *Ann Neurol* **36**: 62–67

Gass A, Moseley IF, Barker GJ *et al* 1996 Lesion discrimination in optic neuritis using high-resolution fat-suppressed fast spin-echo MRI. *Neuroradiology* **38**: 317–321

Gass A, Kitchen N, MacManus DCR *et al* 1997 Trigeminal neuralgia in patients with multiple sclerosis: lesion localization with MRI. *Neurology* **49**: 1142–1144

Gaudet JPC, Hashimoto L, Sadovnick AD, Ebers GC 1995a Is sporadic MS caused by an infection of adolescence and early adulthood? A case-control study of birth order position. *Acta Neurol Scand* **91**: 19–21

Gaudet JPC, Hashimoto L, Sadovnick AD, Ebers GC 1995b A study of birth order and multiple sclerosis in multiplex families. *Neuroepidemiology* **14**: 188–192

Gault F 1894 *De la neuromyélite optique aigue*. Lyon: Thèse de Lyon

Gaupp S, Pitt D, Kuziel WA *et al* 2003 Experimental autoimmune encephalomyelitis (EAE) in CCR2(–/–) mice: susceptibility in multiple strains. *Am J Pathol* **162**: 139–150

Gausas J, Paterson PY, Day ED, Dal Canto MC 1982 Intact B-cell activity is essential for complete expression of experimental allergic encephalomyelitis in Lewis rats. *Cell Immunol* **72**: 360–366

Gautam AM, Lock CB, Smilek DE *et al* 1994 Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules: implications in induction of autoimmunity. *Proc Natl Acad Sci USA* **91**: 767–771

Gautam AM, Liblau R, Chelvanayagam G *et al* 1998 A viral peptide with limited homology to a self peptide can induce clinical signs of experimental autoimmune encephalomyelitis. *J Immunol* **161**: 60–64

Gauthier S, Bharanidharan P, Stazzone L *et al* 2003 Treatment of relapsing remitting interferon/glatiramer acetate unresponsive patients with pulse cyclophosphamide. *Neurology* **60**: A148

Gautier-Smith PC 1973 Lhermitte's sign in subacute combined degeneration of the cord. *J Neurol Neurosurg Psychiatry* **36**: 861–863

Gawne-Cain M, O'Riordan JI, Thompson AJ *et al* 1997 Multiple sclerosis lesion detection in the brain: a comparison of fast fluid-attenuated inversion recovery and conventional T_2 weighted dual spin echo. *Neurology* **49**: 364–370

Gay D, Esiri M 1991 Blood-brain barrier damage in acute multiple sclerosis plaques: an immunocytochemical study. *Brain* **114**: 557–572

Gay FW, Drye TJ, Dick GW, Esiri MM 1997 The application of multifactorial cluster analysis in the staging of plaques in early multiple sclerosis: identification and characterization of primary demyelinating lesion. *Brain* **120**: 1461–1483

Gayou A, Brochet B, Dousset V 1997 Transitional progressive multiple sclerosis: a clinical and imaging study. *J Neurol Neurosurg Psychiatry* **63**: 396–398

Gbadamosi J, Munchau A, Weiller C, Schafer H 2003a Severe heart failure in a young multiple sclerosis patient. *J Neurol* **250**: 241–242

Gbadamosi J, Buhmann C, Tessmer W *et al* 2003b Effects of mitoxantrone on multiple sclerosis patients' lymphocyte subpopulations and production of immunoglobulin, TNF-alpha and IL-10. *Eur Neurol* **49**: 137–141

Ge Y, Grossman RI, Udupa JK *et al* 2000 Brain atrophy in relapsing–remitting multiple sclerosis and secondary progressive multiple sclerosis: longitudinal data analysis. *Radiology* **214**: 665–670

Gean-Marton AD, Venzia LG, Marton KL *et al* 1991 Abnormal corpus callosum: a sensitive and specific indicator of multiple sclerosis. *Radiology* **180**: 215–221

Geisler MW, Sliwinski M, Coyle PK *et al* 1996 The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis. *Arch Neurol* **53**: 185–188

Gelati M, Corsini E, De Rossi M *et al* 2002 Methylprednisolone acts on peripheral blood mononuclear cells and endothelium in inhibiting migration phenomena in patients with multiple sclerosis. *Arch Neurol* **59**: 774–780

Genain CP, Lee-Parritz D, Nguyen M-H *et al* 1994 In healthy primates, circulating autoreactive T cells mediate autoimmune disease. *J Clin Invest* **94**: 1339–1345

Genain CP, Abel K, Belmar N *et al* 1996 Late complications of immune deviation therapy in a nonhuman primate. *Science* **274**: 2054–2057

Genain CP, Cannella B, Hauser SL, Raine CS 1999 Identification of autoantibodies associated with myelin damage in multiple sclerosis. *Nature Med* **5**: 170–175

Genoud S, Lappe-Siefke C, Goebbels S *et al* 2002 Notch1 control of oligodendrocyte differentiation in the spinal cord. *J Cell Biol* **158**: 709–718

Gentiloni N, Schiavino D, Della Corte F *et al* 1992 Neurogenic pulmonary edema: a presenting symptom in multiple sclerosis. *Ital J Neurol Sci* **13**: 435–438

Geny C, Pradat P F, Yulis J *et al* 1992 Hypothermia, Wernicke encephalopathy and multiple sclerosis. *Acta Neurol Scand* **86**: 632–634

Georgi W 1961 Multiple sklerose: pathologisch-anatomische Befund multipler sklerose bei klinisch nicht diagnostizierten Krankheiten. *Schweizer Med Wochenschr* **91**: 605–607

Georgiev D, Milanov I 1994 Epidemiological survey of multiple sclerosis in Bulgaria. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 184–189

Geren BB 1954 The formation from the Schwann cell surface of myelin in the peripheral nerves of chick embryos. *Exp Cell Res* **7**: 558–562

Germain RN 1994 MHC-dependent antigen processing and peptide presentation: providing ligands for T lymphocyte activation. *Cell* **76**: 287–299

Gerritse K, Deen C, Fasbender M *et al* 1994 The involvement of specific anti myelin basic protein antibody-forming cells in multiple sclerosis immunopathology. *J Neuroimmunol* **49**: 153–159

Gerritse K, Laman JD, Noelle RJ *et al* 1996 CD40-CD40 ligand interactions in experimental allergic encephalomyelitis and multiple sclerosis. *Proc Natl Acad Sci USA* **93**: 2499–2504

Gervais A, Gaillard O, Plassart E *et al* 1998 Apolipoprotein E polymorphism in multiple sclerosis. *Ann Clin Biochem* **35**: 135–136

Gessain A, Gout O 1992 Chronic myelopathy associated with human T-lymphotropic virus type 1 (HTLV-1). *Ann Intern Med* **117**: 933–946

Geurts JJG, Wolswijk G, Bo L *et al* 2003 Altered expression patterns of group I and II metabotropic glutamate receptors in multiple sclerosis. *Brain* **126**: 1755–1766

Geurts JJ, Bo L, Pouwels PJ *et al* 2005a Cortical lesions in multiple sclerosis: combined postmortem MR imaging and histopathology. *Am J Neuroradiol* **26**: 572–577

Geurts JJ, Pouwels PJ, Uitdehaag BM *et al* 2005b Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion–recovery MR imaging. *Radiology* **236**: 254–260

Geuze HJ 1998 The role of endosomes and lysosomes in MHC class II functioning. *Immunol Today* **19**: 282–287

Ghabanbasani MZ, Gu XX, Spaaaepen M *et al* 1995 Importance of HLA-DRB1 and DQA1 genes and of the amino acid polymorphisms in the functional domain of DRB1 chain in multiple sclerosis. *J Neuroimmunol* **59**: 77–82

Ghadirian P, Dadgostar B, Azani R, Maisonneuve P 2001 A case-control study of the association between socio-economic, lifestyle and medical history factors and multiple sclerosis. *Can J Public Health* **92**: 281–285

Ghalie RG, Mauch E, Edan G *et al* 2002 A study of therapy-related acute leukemia after mitoxantrone therapy for multiple sclerosis. *Mult Scler* **8**: 441–445

Ghatak NR 1992 Occurrence of oligodendrocytes within astrocytes in demyelinating lesions. *J Neuropathol Exp Neurol* **51**: 40–46

Ghatak NR, Hirano A, Doron Y, Zimmerman HM 1973 Remyelination in multiple sclerosis with peripheral type myelin. *Arch Neurol* **29**: 262–267

Ghatak NR, Hirano A, Lijtmaer H, Zimmerman HM 1974 Asymptomatic demyelinated plaque in the spinal cord. *Arch Neurol* **30**: 484–486

Ghawche F, Destée A 1990 Hypothermie et sclérose en plaques. Un cas avec trois épisodes d'hypothermie transitoire. *Rev Neurol* **146**: 767–769

Ghezzi A 1999 Sexuality and multiple sclerosis. *Scand J Sexol* **2**: 125–140

Ghezzi A, Caputo D 1981 Pregnancy: a factor influencing the course of multiple sclerosis? *Eur Neurol* **20**: 115–117

Ghezzi A, Di Falco M, Locatelli C *et al* 1989 Clinical controlled randomized trial of azathioprine in multiple sclerosis. In: Gonsette RE, Delmotte P (eds) *Recent Advances in Multiple Sclerosis Therapy.* Amsterdam: Elsevier.

Ghezzi A, Montanini R, Basso PF *et al* 1990 Epilepsy in multiple sclerosis. *Eur Neurol* **30**: 218–223

Ghezzi, A, Deplano V, Faroni J *et al* 1997 Multiple sclerosis in childhood: clinical features of 149 cases. *Mult Scler* **3**: 43–46

Ghezzi A, Martinelli V, Torri V *et al* 1999 Long term follow up of optic neuritis: the risk of developing multiple sclerosis, its outcome and the prognostic role of paraclinical tests. *J Neurol* **246**: 770–775

Ghezzi A, Martinelli V, Rodegher M *et al* 2000 The prognosis of idiopathic optic neuritis. *Neurol Sci* **21(Suppl)**: 865–869

Ghezzi A, Pozzilli C, Liguori M, Marrosu MG 2002 Prospective study of multiple sclerosis with early onset. *Mult Scler* **8**: 115–118

Ghezzi A, Bergamaschi R, Martinelli V *et al* 2004 Clinical characteristics, course and prognosis of relapsing Devic's Neuromyelitis Optica. *J Neurol* **251**: 47–52

Ghezzi A, Amato MP, Capobianco M *et al* 2005 Disease-modifying drugs in childhood–juvenile multiple sclerosis: results of an Italian co-operative study. *Mult Scler* **11**: 420–424

Giang DW, Poduri KR, Eskin TA *et al* 1992 Multiple sclerosis masquerading as a mass lesion. *Neuroradiology* **34**: 150–154

Gianola S, Rossi F 2004 GAP-43 overexpression in adult mouse Purkinje cells overrides myelin-derived inhibition of neurite growth. *Eur J Neurosci* **19**: 819–830

Gibson J, Frank A 2002 Supporting individuals with disabling multiple sclerosis. *J R Soc Med* **95**: 580–586

Gideon P, Henriksen O, Sperling B *et al* 1992 Early time course of N-acetylaspartate, creatine and phosphocreatine, and compounds containing choline in the brain after acute stroke: a proton magnetic resonance spectroscopy study. *Stroke* **23**: 1566–1572

Giedraitis V, Modin H, Callander M *et al* 2003 Genome-wide TDT analysis in a localized population with a high prevalence of multiple sclerosis indicates the importance of a region on chromosome 14q. *Genes Immun* **4**: 559–563

Gieffers J, Pohl D, Treib J *et al* 2001 Presence of *Chlamydia pneumoniae* DNA in the cerebral spinal fluid is a common phenomenon in a variety of neurological diseases and not restricted to multiple sclerosis. *Ann Neurol* **49**: 585–589

Giegerich G, Pette M, Meinl E *et al* 1992 Diversity of T cell receptor α and β chain genes expressed by human T cells specific for similar myelin basic protein peptide/major histocompatibility complexes. *Eur J Immunol* **22**: 753–758

Giess R, Maurer M, Linker R *et al* 2002a Association of a null mutation in the CNTF gene with early onset of multiple sclerosis. *Arch Neurol* **59**: 407–409

Giess R, Maurer M, Pohl D 2002b A null mutation in the CNTF gene is associated with early onset of multiple sclerosis. *Arch Neurol* 59: 407–409

Gijbels K, Masure S, Carton H, Opdennakker G 1992 Gelatinase in the cerebrospinal fluid of patients with multiple sclerosis and other inflammatory neurological disorders. *J Neuroimmunol* **41**: 29–34

Gijbels K, Galardy RE, Steinman L 1994 Reversal of experimental autoimmune encephalomyelitis with a hydroxamate inhibitor of matrix metalloproteases. *J Clin Invest* **94**: 2177–2182

Gilbert JJ, Sadler M 1983 Unsuspected multiple sclerosis. *Arch Neurol* **40**: 533–536

Gilden DH 2002 A search for virus in multiple sclerosis. *Hybrid Hybridomics* **21**: 93–97

Gilden DH, Burgoon MP, Kleinschmidt-DeMasters BK *et al* 2001 Molecular immunological strategies to identify antigens and B-cell responses unique to multiple sclerosis. *Arch Neurol* **58**: 43–48

Gilgun-Sherki Y, Panet H, Melamed E, Offen D 2003 Riluzole suppresses experimental autoimmune encephalomyelitis: implications for the treatment of multiple sclerosis. *Brain Res* **989**: 196–204

Gilgun-Sherki Y, Melamed E, Offen D 2004 The role of oxidative stress in the pathogenesis of multiple sclerosis: the need for effective antioxidant therapy. *J Neurol* **251**: 261–268

Gill KP, Chia YW, Henry MM Shorvon PJ 1994 Defecography in multiple sclerosis patients with severe constipation. *Radiology* **191**: 553–556

Gillespie JW, Ahram M, Best CJ *et al* 2002 The role of tissue microdissection in cancer research. *Cancer J* **7**: 32–39

Gilli F, Bertolotto A, Sala A *et al* 2004 Neutralizing antibodies against IFN-beta in multiple sclerosis: antagonization of IFN-beta mediated suppression of MMPs. *Brain* **127**: 259–268

Gilliatt RW 1982 Electrophysiology of peripheral neuropathies – an overview. *Muscle Nerve* **5**: S108–S116

Gilmore M, Grennan E, 2003 A pilot study of the relationship between multiple sclerosis and the physical environment in northwest Ireland. *Environ Geochem Health* **25**: 157–163

Giobbia M, Carniato A, Scotton PG *et al* 1999 Cytomegalovirus-associated transverse myelitis in a non-immunocompromised patient. *Infection* **27**: 228–230

Giordana MT, Richiardi P, Trevisan E *et al* 2003 Abnormal ubiquitination of axons in normally myelinated white matter in multiple sclerosis brain. *Neuropath Appl Neurobiol* **28**: 35–41

Giovannoni G 1998 Cerebrospinal fluid and serum nitric oxide metabolites in patients with multiple sclerosis. *Mult Scler* **4**: 27–30

Giovannoni G, Goodman A 2005 Neutralizing anti-IFN-beta antibodies: how much more evidence do we need to use them in practice? *Neurology* **65**: 6–8

Giovannoni G, Heales SJR, Silver NC *et al* 1997 Raised serum nitrate and nitrite levels in patients with multiple sclerosis. *Journal of Neurological Science* **145**: 77–81

Giovannoni G, Heales SJ, Land JM, Thompson EJ 1998 The potential role of nitric oxide in multiple sclerosis. *Mult Scler* **4**: 212–216

Giovannoni G, Miller DH, Lossef NA *et al* 2001a Serum inflammatory markers and clinical/MRI markers of disease progression in multiple sclerosis. *J Neurol* **248**: 487–495

Giovannoni G, Thompson AJ, Miller DH, Thompson EJ 2001b Fatigue is not associated with raised inflammatory markers in multiple sclerosis. *Neurology* **57**: 676–681

Giraudon P, Vincent P, Vuaillat C *et al* 2004 Semaphorin CD100 from activated T lymphocytes induces process extension collapse in oligodendrocytes and death of immature neural cells. *J Immunol* **172**: 1246–1255

Girgrah N, Letarte M, Becker LE *et al* 1991 Localisation of CD44 glycoprotein to fibrous astrocytes in normal appearing white matter and to reactive astrocytes in active lesions in multiple sclerosis. *J Neuropath Exp Neurol* **50**: 779–792

Giroud M, Guard O, Dumas R 1988 Anomalies cardio-respiratoires dans la sclérose en plaques. *Rev Neurol* **14**: 284–288

Giubilei F, Antonini G, Di Legge S *et al* 2002 Blood cholesterol and MRI activity in first clinical episode suggestive of multiple sclerosis. *Acta Neurol Scand* **106**: 109–112

Giulian D, Johnson B, Krebs JF *et al* 1991 A growth factor from neuronal cell lines stimulates myelin protein synthesis in mammalian brain. *J Neurosci* **11**: 327–336

Giunti D, Borsellino G, Benelli R *et al* 2003 Phenotypic and functional analysis of T cells homing into the CSF of subjects with inflammatory diseases of the CNS. *J Leukoytec Biol* **73**: 584–590

Givogri MI, Costa RM, Schonmann V *et al* 2002 Central nervous system myelination in mice with deficient expression of Notch1 receptor. *J Neurosci* **67**: 309–320

Glaser GH, Merritt HH 1952 Effects of corticotrophin (ACTH) and cortisone on disorders of the nervous system. *J Am Med Assoc* **148**: 898–904

Gledhill RF, McDonald WI 1977 Morphological characteristics of central demyelination and remyelination: a single-fiber study. *Ann Neurol* **1**: 552–560

Gledhill RF, Harrison BM, McDonald WI 1973 Pattern of remyelination in the CNS. *Nature* **244**: 443–444

Glick ME, Meshkinpour H, Haldeman S *et al* 1982 Colonic dysfunction in multiple sclerosis. *Gastroenterology* **83**: 1002–1007

Global Advisory Committee on Vaccine Safety, 20–21 June 2002. *Wkly Epidemiol Rec* **77**: 389–394

Gneiss C, Reindl M, Lutterotti A *et al* 2004 Interferon-beta: the neutralizing antibody (NAb) titre predicts reversion to NAb negativity. *Mult Scler* **10**: 507–510

Go T, Imai T 2000 A residual cystic lesion in acute disseminated encephalomyelitis. *Neuroradiology* **42**: 682–684

Goas JY, Marion JL, Missoum A 1983 High dose intravenous methyl prednisolone in acute exacerbations of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **46**: 99

Gobbini MI, Smith ME, Richert ND *et al* 1999 Effect of open label pulse cyclophosphamide therapy on MRI measures of disease activity in five patients with refractory relapsing–remitting multiple sclerosis. *J Neuroimmunol* **99**: 142–149

Goddard DR, Berry M, Butt AM 1999 In vivo actions of fibroblast growth factor-2 and insulin-like growth factor-I on oligodendrocyte development and myelination in the central nervous system. *J Neurosci Res* **57**: 74–85

Goddard DR, Berry M, Kirvell SL, Butt AM 2001 Fibroblast growth factor-2 inhibits myelin production by oligodendrocytes in vivo. *Mol Cell Neurosci* **18**: 557–569

Godfrey DI, Hammond KJL, Poulton LD *et al* 2000 NKT cells: facts, functions and fallacies. *Immunol Today* **21**: 573–583

Goebels N, Hofstetter H, Schmidt S *et al* 2000 Repertoire dynamics of autoreactive T cells in multiple sclerosis patients and healthy subjects: epitope spreading versus clonal persistence. *Brain* **123**: 508–518

Goebels N, Helmchen C, Abel-Horn M *et al* 2001 Extensive myelitis associated with *Mycoplasma pneumoniae* infection: magnetic resonance imaging and clinical long term follow up. *J Neurol* **248**: 204–208

Goedde R, Sawcer S, Boehringer S *et al* 2002 A genome screen for linkage disequilibrium in HLA-DRB1*15-positive Germans with multiple sclerosis based on 4666 microsatellite markers. *Hum Genet* **111**: 270–277

Goertsches R, Villoslada P, Comabella M *et al* 2003 A genomic screen of Spanish multiple sclerosis patients reveals multiple loci associated with the disease. *J Neuroimmunol* **143**: 124–128

Goertsches R, Comabella M, Navarro A *et al* 2005 Genetic association between polymorphisms in the ADAMTS14 gene and multiple sclerosis. *J Neuroimmunol* **164**: 140–147

van der Goes A, Brouwer J, Hoekstra K *et al* 1998 Reactive oxygen species are required for the phagocytosis of myelin by macrophages. *J Neuroimmunol* **92**: 67–75

van der Goes A, Kortekaas M, Hoekstra K *et al* 1999 The role of anti-myelin (auto)-antibodies in the phagocytosis of myelin by macrophages. *J Neuroimmunol* **101**: 61–67

Goffette S, van Pesch V, Vanoverschelde JL *et al* 2005 Severe delayed heart failure in three multiple sclerosis patients previously treated with mitoxantrone. *J Neurol* [epub ahead of print]

Gogate N, Verma L, Min Zhau J *et al* 1994 Plasticity in the adult human oligodendrocyte lineage. *J Neurosci* **14**: 4571–4587

Gogolin KJ, Kolaga VJ, Baker L *et al* 1989 Subtypes of HLA-DQ and -DR defined by DQB1 and DRB1 RFLPs: allele frequency in the general population and in insulin dependent diabetes (IDMM) and multiple sclerosis patients. *Ann Hum Genet* **353**: 357–360

Gold DP, Offner H, Sun D *et al* 1991 Analysis of T cell receptor β chains in Lewis rats with experimental allergic encephalomyelitis: conserved complementary determining region 3. *J Exp Med* **174**: 1467–1476

Gold MS, Zhang L, Wrigley DL, Traub RJ 2002 Prostaglandin E(2) modulates TTX-R I(Na) in rat colonic sensory neurons. *J Neurophysiol* 88: 1512–1522

Gold R, Linington C 2002 Devic's disease: bridging the gap between laboratory and clinic. *Brain* **125**: 1425–1427

Gold R, Schmied M, Giegerich G *et al* 1994 Differentiation between cellular apoptosis and necrosis by combined use of *in situ* tailing and nick translation techniques. *Lab Invest* **71**: 219–225

Gold R, Schmied M, Tontsch U *et al* 1996 Antigen presentation by astrocytes primes rat T lymphocytes for apoptotic cell death: a model for T-cell apoptosis *in vivo*. *Brain* **119**: 651–659

Gold R, Buttgereit F, Toyka KV 2001 Mechanism of action of glucocorticosteroid hormones: possible implications for therapy of neuroimmunological disorders. *J Neuroimmunol* **117**: 1–8

Goldacre MJ, Wotton CJ, Seagroatt V, Yeates D 2004 Multiple sclerosis after infectious mononucleosisis: record linkage study. *J Epidemiol Commun Hlth* **58**: 1032–1035

Goldberg ID, Kurland LT 1962 Mortality in 33 countries for diseases of the nervous system. *World Neurol* **3**: 444–465

Goldberg JL, Barnes BA 2000 Nogo in nerve regeneration. *Nature* **403**: 369–370

Goldberg SH, van der Meer P, Hesselgesser J *et al* 2001 CXCR3 expression in human central nervous system diseases. *Neuropathol Appl Neurobiol* **27**: 127–138

Golde S, Chandran S, Brown GC, Compston DAS 2002 Different pathways for iNOS-mediated toxicity *in vitro* dependent on neuronal maturation and NMDA-receptor expression. *J Neurochem* **82**: 269–282

Golde S, Coles AJ, Lindquist JA, Compston DAS 2003 Decreased iNOS-synthesis mediates dexamethasone induced protection of neurones from inflammatory injury in vitro. *Eur J Neurosci* **18**: 2527–2537

Golden GS, Woody RC 1987 The role of nuclear magnetic imaging in the diagnosis of MS in children. *J Neurol* **37**: 689–693

Goldstein B 1946 Two cases of disseminated sclerosis in African natives. *East Afr Med J* **23**: 170–173

Goldstein I, Lue TF, Padma-Nathan H *et al* 1998 Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med* **338**: 1397–404

Golgi C 1894 *Untersuchungen über den Feineren bau des Centralen und Peripherischen nervensystems*. Jena: von Gustav Fischer

Gollan L, Salomon D, Salzer JL, Peles E 2003 Caspr regulates the processing of contactin and inhibits its binding to neurofascin. *J Cell Biol* **163**: 1213–1218

Gomaa A, Shalaby M, Osman M *et al* 1996 Topical treatment of erectile dysfunction: randomised double blind placebo controlled trial of cream containing aminophylline, isosorbide dinitrate, and co-dergocrine mesylate. *Br Med J* **312**: 1512–1515

Gombert J-M, Herbelin A, Tancrède-Bohin E *et al* 1996 Early quantitative and functional deficiency of $NK1^+$-like thymocytes in the NOD mouse. *Eur J Immunol* **26**: 2989–2998

Gomes WA, Mehler MF, Kessler JA 2003 Transgenic overexpression of BMP4 increases astroglial and decreases oligodendroglial lineage commitment. *Dev Biol* **255**: 164–177

Gomez-Lira M, Moretto G, Bonamini D *et al* 2002 Myelin oligodendrocyte glycoprotein polymorphisms and multiple sclerosis. *J Neuroimmunol* **133**: 241–243

Gomez-Lira M, Liguouri M, Magnani C *et al* 2003 CD45 and multiple sclerosis: the exon 4 C77G polymorphism (additional studies and meta-analysis) and new markers. *J Neuroimmunol* **140**: 216–221

Gondim FdeA, Thomas FP 2001 Episodic hyperlibidinism in multiple sclerosis. *Mult Scler* **7**: 67–70

Gonen O, Catalaa I, Babb JS *et al* 2000 Total brain N-acetylaspartate: a new measure of disease load in MS. *Neurology* **54**: 15–19

Gonsette R, Andre-Balisaux G, Delmotte P 1966 La permeabilité des vaisseaux cerebraux VI Demyelinisation experimentale provoquée par des substances agissant sur la barriére hematoencephalique. *Acta Neurol Belg* **66**: 247–262

Gonsette RE 2004 Combination therapy for multiple sclerosis. *The International MS Journal* **11**: 10–21

Gonzalez CF, Swirsky-Sacchetti T, Mitchell D *et al* 1994 Distributional patterns of multiple sclerosis brain lesions. Magnetic resonance imaging – clinical correlation. *Journal of Neuroimaging* **4**: 188–195

Gonzalez-Scarano F, Grossman RI, Galetta S *et al* 1987 Multiple sclerosis disease activity correlates with gadolinium-enhanced magnetic resonance imaging. *Ann Neurol* **21**: 300–306

Good K, Clark CM, Oger J *et al* 1992 Cognitive impairment and depression in mild multiple sclerosis. *J Nerv Mental Disease* **180**: 730–732

Goodin DS 2003 Interferons in relapsing remitting multiple sclerosis. *Lancet* **361**: 1821; author reply 1823–1824

Goodin DS, Ebers GC, Johnson KP *et al* 1999 The relationship of MS to physical trauma and psychological stress – Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **52**: 1737–1745

Goodin DS, Frohman EM, Garmany GP Jr *et al* 2002 Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* **58**: 169–178

Goodin DS, Arnason B, Coyle P *et al* 2003 The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis – Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **61**: 1332–1338

Goodkin DE 1991 Inter and intra observer variablity for grades 1.0–3.5 of the Kurtzke Expanded Disability Status Scale (EDSS). *Neurology* **42**: 859–863

Goodkin DE 1994 Interferon beta-1b. *Lancet* **344**: 1057–1060

Goodkin DE 2000 Interferon beta-1b in secondary progressive MS: clinical and MRI results of a 3-year randomized controlled trial (abstract) **54**: 2352

Goodkin DE, Hertsgaard D 1989 Seasonal variation of multiple sclerosis exacerbations in North Dakota. *Arch Neurol* **46**: 1015–1018

Goodkin DE, Hertsgaard D, Rudick RA 1989 Exacerbation notes and adherence to

disease type in a prospectively followed-up population with multiple sclerosis: implications for clinical trials. *Arch Neurol* 46: 1107–1112

Goodkin DE, Bailly PC, Teetzen ML *et al* 1991 The efficacy of azathioprine in relapsing remitting multiple sclerosis. *Neurology* **41**: 20–25

Goodkin DE, Cookfair D, Wende K *et al* 1992 Inter- and intra-rater scoring agreement using grades 1.0 to 3.5 of the Kurtzke Expanded Disability Status Scale (EDSS). Multiple Sclerosis Collaborative Research Group. *Neurology* **42**: 859–863

Goodkin DE, Rudick RA, VanderBrug Medendorp S *et al* 1995 Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progresssive multiple sclerosis. *Ann Neurol* **37**: 30–40

Goodkin DE, Rudick RA, VanderBrug Medendorp S *et al* 1996 Low-dose oral methotrexate in chronic progressive multiple sclerosis: analyses of serial MRIs. *Neurology* **47**: 1153–1157

Goodkin DE, Shulman M, Winkelhake J *et al* 2000 A phase I trial of solubilized DR2:MBP84–102 (AG284) in multiple sclerosis. *Neurology* **54**: 1414–1420

Goodman AD, Miller DH 2002 Infections and MS: clinical trials move to center stage. *Neurology* **58**: 7–8

Goodman AD, Mock DJ, Powers JM *et al* 2003 Human herpesvirus 6 genome and antigen in acute multiple sclerosis lesions. *J Infect Dis* **187**: 1365–1376

Goodnow CC 1992 Transgenic mice and analysis of B-cell tolerance. *Ann Rev Immunol* **10**: 489–518

Gore J 2003 Out of the shadows – MRI and the Nobel Prize. *N Engl J Med* **349**: 2290–2292

Goris A, Epplen C, Fiten P *et al* 1999 Analysis of an IFN gamma gene (IFNγ) polymorphism in multiple sclerosis in Europe: effect of population structure on association with disease. *J Interferon Cytokine Res* **19**: 1037–1046

Goris A, Heggarty S, Marrosu MG *et al* 2002 Linkage disequlibrium analysis of chromosome 12q14–15 in multiple sclerosis: delineation of a 118-kb interval around interferon-gamma (IFNG) that is involved in male versus female differential susceptibility. *Genes Immun* **3**: 470–476

Goris A, Sawcer SJ, Vandenbroeck K *et al* 2003 New candidate loci for multiple sclerosis susceptibility revealed by a whole genome association screen in a Belgian population. *J Neuroimmunol* **143**: 65–69

Gorodetsky C, Najera R, Rangel BE *et al* 1986 Immunogenetic profile of multiple sclerosis in Mexicans. *Hum Immunol* **16**: 364–374

Gosselink R, Kovacs L, Ketelaer P *et al* 2000 Respiratory muscle weakness and respiratory muscle training in severely disabled multiple sclerosis patients. *Arch Phys Med Rehab* **81**: 747–751

Goswami KKA, Randall RE, Lange LS, Russell WC 1987 Antibodies against the paramyxovirus SV5 in cerebrospinal fluids of some multiple sclerosis patients. *Nature* **327**: 244–247

Gottschalk M, Kumpfel T, Flachenecker P *et al* 2005 Fatigue and regulation of the hypothalamo–pituitary–adrenal axis in multiple sclerosis. *Arch Neurol* **62:** 277–280

Gould E, Tanapat P, McEwen BS *et al* 1998 Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proc Natl Acad Sci USA* **95**: 3168–3171

Gould ES, Bird AC, Leaver PK, McDonald WI 1977 Treatment of optic neuritis by retrobulbar injection of triamcinolone. *Br Med J* **i**: 1495–1497

Gould HJ 1982 Disabilities and how to live with them: multiple sclerosis. *Lancet* **ii**: 1208–1210

Gould HJ, England JD, Liu ZP, Levinson SR 1998 Rapid sodium channel augmentation in response to inflammation induced by complete Freund's adjuvant. *Brain Res* **802**: 69–74

Goureau O, Amiot F, Dautry F, Courtois Y 1997 Control of nitric oxide production by endogenous TNF-alpha in mouse retinal pigmented epithelial and Muller glial cells. *Biochem Biophys Res Commun* **240**: 132–135

Gourie-Devi M, Nagaraja D 1982 Multiple sclerosis in south India. In: Kuroiwa Y, Kurland L (ed.) *Multiple Sclerosis East and West*. Fukoka: Kyushu University Press, pp. 135–148

Gout O, Théodorou I, Liblau R, Lyon-Caen O 1997 Central nervous system demyelination after recombinant hepatitis B vaccination: report of 25 cases. *Neurology* **48 (Suppl)**: A424

Govaerts A, Gony J, Martin-Mondiere C *et al* 1985 HLA in multiple sclerosis: population family studies. *Tissue Antigens* **25**: 187–199

Goverman J, Woods A, Larson L *et al* 1993 Transgenic mice that express a myelin basic protein-specific T cell receptor develop spontaneous autoimmunity. *Cell* **72**: 551–560

Gowers WR 1888 *A Manual of Disease of the Nervous System*. London: J. & A. Churchill, pp. 507–519

Gowers WR 1893 *A Manual of Disease of the Nervous System*. 2nd edn. London: J. & A. Churchill, Vol II, p. 1069

Graesser D, Solowiej A, Bruckner M *et al* 2002 Altered vascular permeability and early onset of experimental autoimmune encephalomyelitis in PECAM-1-deficient mice. *J Clin Invest* **109**: 383–392

Graff-Radford NR, Rizzo M 1987 Neglect in a patient with multiple sclerosis. *Eur Neurol* **26**: 100–103

Grafman J, Rao S, Bernardin L, Leo GJ 1991 Automatic memory processes in patients with multiple sclerosis. *Arch Neurol* **48**: 1072–1075

Graham C, Kirk C, Nevin N *et al* 1993 Lack of association between myelin basic protein gene microsatellite and multiple sclerosis. *Lancet* **341**: 1596

Graham EM, Ellis CJK, Sanders MD, McDonald WI 1986 Optic neuropathy in sarcoidosis. *J Neurol Neurosurg Psychiatry* **49**: 756–763

Gran B, Bielekova B, McFarland H *et al* 2000a Development of multiple sclerosis after hepatitis B vaccination: an immunologic case report. *Neurology* **54** (suppl 3): A164

Gran B, Tranquill LR, Chen M *et al* 2000b Mechanisms of immunomodulation by glatiramer acetate. *Neurology* **55**: 1704–1714

Gran B, Zhang G-X, Yu S *et al* 2002 IL-12p35-deficient mice are susceptible to experimental autoimmune encephalomyelitis: evidence for redundancy in the IL-12 system in the induction of central nervous system autoimmune demyelination. *J Immunol* **169**: 7104–7110

GrandPré T, Nakamura F, Vartanian T, Strittmatter SM 2000 Identification of the Nogo inhibitor of axon regeneration as a Reticulon protein. *Nature* **403**: 439–444

Granieri E, Casetta I 1997 Common childhood and adolescent infections and multiple sclerosis. *Neurology* **49 (Suppl 2)**: S42–S54

Granieri E, Rosati G 1982 Italy: a medium- or high-risk area for multiple sclerosis? An epidemiological study in Barbagia, Sardinia, southern Italy. *Neurology* **32**: 466–472

Granieri E, Tola MR 1994 Experience in multiple sclerosis epidemiology in Italy. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 184–189

Granieri E, Rosati G, Tola R *et al* 1983 The frequency of multiple sclerosis in Mediterranean Europe: an incidence and prevalence study in Barbagia, Sardinia, insular Italy. *Acta Neurol Scand* **68**: 84–89

Granieri E, Tola R, Paolino E *et al* 1985 The frequency of multiple sclerosis in Italy: a descriptive study in Ferrara. *Ann Neurol* **17**: 80–84

Granieri E, Casetta I, Tola M *et al* 1993 Multiple sclerosis: does epidemiology contribute to providing etiological clues? *J Neurol Sci* **115 (Suppl)**: S16–S23

Granieri E, Malagu S, Casetta I *et al* 1996 Multiple sclerosis in Italy: a reappraisal of incidence and prevalence in Ferrara. *Arch Neurol* **53**: 793–798

Granieri E, Casetta I, Govoni V *et al* 2000 The increasing incidence and prevalence of MS in a Sardinian province. *Neurology* **55**: 842–848

Grant I, McDonald WI, Trimble MR *et al* 1984 Deficient learning and memory in early and middle phases of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **47**: 250–255

Grant I, Brown GW, Harris T *et al* 1989 Severely threatening events and marked life difficulties preceding onset or exacerbation of multiple sclerosis. *J Neurol Neurosurg Psych* **52**: 8–13

Grant RM, Carver AD, Sloan RL 1998 Multiple sclerosis in Fife. *Scot Med J* **43**: 44–47

Grasso MG, Lubich S, Guidi L *et al* 2000 Cerebellar deficit and respiratory

impairment: a strong association in multiple sclerosis? *Acta Neurol Scand* **101**: 98–103
Graumann U, Reynolds R, Steck AJ, Schaeren-Wiemers, N 2003 Molecular changes in normal appearing white matter in multiple sclerosis are characteristic of neuroprotective mechanisms against hypoxic insult. *Brain Pathol* **13**: 554–573
Graves MC 1981 Gastric outlet obstruction in a patient with multiple sclerosis. *Ann Neurol* **10**: 397–398
Graveson GS 1950 Syphilitic optic neuritis. *J Neurol Neurosurg Psychiatry* **13**: 216–224
Gray F, Chimelli L, Mohr M *et al* 1991 Fulminating multiple sclerosis-like leukoencephalopathy revealing human immunodeficiency virus infection. *Neurology* **41**: 105–109
Greco A, Minghetti L, Sette G *et al* 1999 Cerebrospinal fluid isoprostane shows oxidative stress in patients with multiple sclerosis. *Neurology* **53**: 1876–1879
Green AJ, Barcellos LF, Rimmler JB *et al* 2001 Sequence variation in the transforming growth factor-beta 1 (TGFβ1) gene and multiple sclerosis susceptibility. The Multiple Sclerosis Genetics Group. *J Neuroimmunol* **116**: 116–124
Green DR, Beere HM 2000 Gone but not forgotten. *Nature* **405**: 28–29
Greenberg HS, Werness SAS, Pugh JE, Andrews RO, Anderson DJ, Domino EF 1994 Short term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clin Pharmacol Ther* **51**: 292–296
Greenberg SJ, Ehrlich GD, Abbott MA *et al* 1989 Detection of sequences homologous to human retroviral DNA in multiple sclerosis by gene amplification. *Proc Natl Acad Sci USA* **86**: 2878–2882
Greenfield JG, Carmichael EA 1925 *The Cerebrospinal Fluid in Clinical Diagnosis*. London: Macmillan
Greenfield JG, King LS 1936 Histopathology of the cerebral lesions in disseminated sclerosis. *Brain* **59**: 445–458
Greenspun B, Stineman M, Agri R 1987 Multiple sclerosis and rehabilitation outcome. *Arch Phys Med Rehab* **68**: 434–437
Greenstein JL, McFarland HF, Mingioli ES, McFarlin DE 1984 The lymphoproliferative response to measles virus in twins with multiple sclerosis. *Ann Neurol* **15**: 79–84
Greenwood K, Butt AM 2003 Evidence that perinatal and adult NG2-glia are not conventional oligodendrocyte progenitors and do not depend on axons for their survival. *Mol Cell Neurosci* **23**: 544–558
Greer JM, Pender MP 2005 The presence of glutamic acid at positions 71 or 74 in pocket 4 of the HLA-DRbeta1 chain is associated with the clinical course of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **76**: 656–662
Greer JM, Sobel RA, Sette A *et al* 1996 Immunogenic and encephalitogenic epitope clusters of myelin proteolipid protein. *J Immunol* **156**: 371–379
Greer JM, Csurhes PA, Cameron KD *et al* 1997 Increased immunoreactivity to two overlapping peptides of myelin proteolipid protein in multiple sclerosis. *Brain* **120**: 1447–1460
Gregori N, Proschel C, Noble M, Mayer-Proschel M 2002 The tripotential glial-restricted precursor (GRP) cell and glial development in the spinal cord: generation of bipotential oligodendrocyte-type-2 astrocyte progenitor cells and dorsal-ventral differences in GRP cell function. *J Neurosci* **22**: 248–256
Grenman R 1985 Involvement of the audiovestibular system in multiple sclerosis. *Acta Oto-Laryngologica* **420 (Suppl)**: 1–95
Gresty MA, Eli JJ, Findley LJ 1982 Acquired pendular nystagmus: its characteristics, localising value and pathophysiology. *J Neurol Neurosurg Psychiatry* **45**: 431–439
Greter M, Heppner FL, Lemos MP *et al* 2005 Dendritic cells permit immune invasion of the CNS in an animal model of multiple sclerosis. *Nature Med* **11**: 328–334
Grewal IS, Foellmer HG, Grewal KD *et al* 1996 Requirement for CD40 ligand in costimulation induction, T cell activation, and experimental allergic encephalomyelitis. *Science* **273**: 1864–1867
Grewal IS, Foellmer HG, Grewal KD *et al* 2001 CD62L is required on effector cells for local interactions in the CNS to cause myelin damage in experimental allergic encephalomyelitis. *Immunity* **14**: 291–302
Grewel RP, Petronas N, Barton NW 1991 Late onset globoid cell leukodystrophy. *J Neurol Neurosurg Psychiatry* **54**: 1011–1012
Grieb P, Ryba M, Stelmasiak Z *et al* 1994 Cladribine and multiple sclerosis (letter). *Lancet* **344**: 538
Griffin CM, Chard DT, Parker GJM *et al* 2002a The relationship between lesion and normal appearing brain tissue abnormalities in early relapsing remitting MS. *J Neurol* **249**: 193–199
Griffin CM, Dehmeshki J, Chard DT *et al* 2002b TI histograms of normal-appearing brain tissue are abnormal in early relapsing–remitting multiple sclerosis. *Mult Scler* **8**: 211–216
Griffin JW, Goren E, Schaumberg H, Engel WK, Loriaux L 1977 Adrenomyeloneuropathy: a probable variant of adrenoleukodystrophy. *Neurology* 27: 1107–1113
Griffin JW, Li CY, Macko C *et al* 1996 Early nodal changes in the acute motor axonal neuropathy pattern of the Guillain–Barre syndrome. *J Neurocytology* **25**: 33–51
Grigoresco D 1932 Contribution à l'étude des troubles dûs à des lésions des noyaux gris dans la sclérose en plaques. *Rev Neurol* **58**: 27–45
Grima B, Zelenika D, Pessac B 1992 A novel transcript overlapping the myelin basic protein gene. *J Neurochem* **59**: 2318–2323
Grima DT, Torrance GW, Francis G *et al* 2000 Cost and health related quality of life consequences of multiple sclerosis. *Mult Scler* **6**: 91–98
Grimaldi LM, Salemi G, Grimaldi G *et al* 2001 High incidence and increasing prevalence of MS in Enna (Sicily), southern Italy. *Neurology* **57**: 1891–1893
Grimaldi LM, Pincherle A, Martinelli-Boneschi F *et al* 2003 An MRI study of *Chlamydia pneumoniae* infection in Italian multiple sclerosis patients. *Mult Scler* **9**: 467–471
Grimaud J, Millar J, Thorpe JW *et al* 1995 Signal intensity on MRI of basal ganglia in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **59**: 306–308
Grinspan JB, Stern JL, Franceschini B, Pleasure D 1993 Trophic effects of basic fibroblast growth factor (bFGF) on differentiated oligodendroglia: a mechanism for regeneration of the oligodendroglial lineage. *J Neurosci Res* **36**: 672–680
Grisold W, Lutz D, Wolf D 1980 Necrotising myelopathy associated with acute lymphoblastic leukaemia. *Acta Neuropathol* **49**: 231–235
Gronlie SA, Myrvoll E, Hansen G, Grønning M, Mellgren SI 2000 Multiple sclerosis in north Norway, and its first appearance in an indigenous population. *J Neurol* **247**: 129–133
Grønning M 1994 The epidemiology of multiple sclerosis in Norway: a 50 year follow-up in a stable population. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 62–66
Grønning M, Mellgren SI 1985 Multiple sclerosis in the two northernmost counties of Norway. *Acta Neurol Scand* **72**: 321–327
Grønning M, Riise T, Kvåle G *et al* 1991 Incidence of multiple sclerosis in Hordaland, western Norway: a fluctuating pattern. *Neuroepidemiology* **10**: 53–61
Gronseth GS, Ashman EJ 2000 Practice parameter: the usefulness of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* **54**: 1720–1725
Gross K, Kokk A, Kaasik AE 1993 Prevalence of MS in south Estonia. Evidence of a new border of the Fennoscandian focus. *Acta Neurol Scand* **88**: 241–246
Grossman M, Robinson KM, Onishi K *et al* 1995 Sentence comprehension in multiple sclerosis. *Acta Neurol Scand* **92**: 324–331
Grossman RI 1994 Magnetization transfer in multiple sclerosis. *Ann Neurol* **36**: 97–99
Grossman RI, Gonzalez-Scarano F, Atlas SW *et al* 1986 Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology* **161**: 721–725
Grossman RI, Braffman BH, Brorson JR *et al* 1988 Multiple sclerosis: serial study of gadolinium-enhanced MR imaging. *Radiology* **169**: 117–122
Grossman RI, Lenkinski RE, Ramer KN *et al* 1992 MR proton spectroscopy in multiple sclerosis. *Am J Neuroradiol* **13**: 1535–1543

Grosz K 1924 Malaria behandlung der multipler Sklerose. *Jahrbucher Psychiatr Neurol* **43**: 198–214

Grouard G, Rissoan M-C, Filgueira L *et al* 1997 The enigmatic plasmacytoid T cells develop into dendritic cells with interleukin (IL)-3 and CD40-ligand. *J Exp Med* **185**: 1101–1111

Groves AK, Barnett SC, Franklin RJM *et al* 1993 Repair of demyelinated lesions by transplantation of purified O-2A progenitor cells. *Nature* **362**: 453–455

Grufferman S, Barton JW, Eby NL 1987 Increased sex concordance of sibling pairs with Behcet's disease, Hodgkin's disease, multiple sclerosis and sarcoidosis. *Am J Epidemiol* **126**: 365–369

Gudmundsson KR 1971 Clinical studies of multiple sclerosis in Iceland. *Acta Neurol Scand* **47 (Suppl 48)**: 1–78

Gudnardottir M, Helgedottir H, Bjarnason O, Jonsdottir K 1964 Virus isolated from the brain of a patient with multiple sclerosis. *Exp Neurol* **9**: 85–95

Guenard V, Frisch G, Wood PM 1996 Effects of axonal injury on astrocyte proliferation and morphology *in vitro*: implications for astrogliosis. *Exp Neurol* **137**: 175–190

Guerini FR, Losciale L, Mediati M *et al* 2000 A polymorphism in the repetitive (TGGA) sequence 5' to the human myelin basic protein gene in Italian multiple sclerosis patients. *J Neurovirol* **6 (Suppl 2)**: S28–S32

Guerini FR, Ferrante P, Losciale L *et al* 2003 Myelin basic protein gene is associated with MS in DR4- and DR5- positive Italians and Russians. *Neurology* **61**: 520–526

Guilhoto LM, Osorio CA, Machado LR *et al* 1995 Pediatric multiple sclerosis: report of 14 cases. *Brain Dev* **17**: 9–12

Guilian D, Johnson B, Krebs JF *et al* 1991 A growth factor from neuronal cell lines stimulates myelin protein synthesis in mammalian brain. *J Neurosci* **11**: 327–336

Guillain G, Bize R 1933 Sur un cas de sclérose en plaques avec torticollis spasmodique. *Rev Neurol* **40**: 133–138

Guillain G, Barré JA, Strohl A 1916 Sur un syndrôme de radiculonervite avec hyperalbuminose du liqid cephalorachidien sans reaction cellulaire, remarqués sur les charactères cliniques et graphiques des reflexes tendineux. *Bull Soc Med Hôpital (Paris)* **40**: 1462–1470

Günther, Schön 1840 Versuche und Bemerkungen über Regeneration der Nerven und Abhängigkeit der peripherischen Nerven von den Centralorganen. *Müllers Arch Anat Physiol Wissenschaftl Med*: 270–286

Guo YP, Gao SF 1983 Concentric sclerosis. In: Tyrer JH, Eadie MJ (eds) *Clinical and Experimental Neurology. Proceedings of the Australian Association of Neurologists*. Sydney: Adis Health Science Press, Vol 19, pp. 67–76

Gupta MK 1987 Myelin basic protein and demyelinating diseases. *Crit Rev Clin Lab Sci* **24**: 287–314

Gupta YK 1984 Gastroparesis with multiple sclerosis. *J Am Med Assoc* **252**: 42

Gupte G, Stonehouse M, Wassmer E *et al* 2003 Acute disseminated encephalomyelitis: a review of 18 cases in childhood. *J Paediatr Child Health* **39**: 336–342

Guseo A, Jellinger K 1975 The significance of perivascular infiltrations in multiple sclerosis. *J Neurol* **211**: 51–60

Guseo A, Jofeju E, Kocsis A 1994 Epidemiology of multiple sclerosis in western Hungary 1957–1992. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 279–286

Gusev E, Boiko A, Lauer K *et al* 1996 Environmental risk factors in MS: a case control study in Moscow. *Acta Neurol Scand* **94**: 386–394

Guthikonda P, Baker J, Mattson DH 1998 Interferon-beta-1-b (IFN-β) decreases induced nitric oxide (NO) production by a human astrocytoma cell line. *J Neuroimmunol* **82**: 133–139

Guthrie TC 1951 Visual and motor changes in patients with multiple sclerosis. *Arch Neurol Psychiatry* **65**: 437–451

Guttmann L 1952 Principles of rehabilitation in disseminated sclerosis. *Br J Phys Med* **15**: 189–191

Guzman NJ, Fang MZ, Tang SS *et al* 1995 Autocrine inhibition of Na+/K(+)-ATPase by nitric oxide in mouse proximal tubule epithelial cells. *J Clin Invest* **95**: 2083–2088

Gveric D, Hanemaaijer R, Newcombe J *et al* 2001 Plasminogen activators in multiple sclerosis lesions: implications for the inflammatory response and axonal damage. *Brain* **124**: 1978–1999

Gveric D, Herrera B, Petzold A *et al* 2003 Impaired fibrinolysis in multiple sclerosis: a role for tissue plasminogen activator inhibitors. *Brain* **126**: 1590–1598

Gyapay G, Morissette J, Vignal A *et al* 1994 The 1993–94 Genethon human genetic linkage map. *Nature Genet* **7**: 246–339

Haahr S, Koch-Henriksen N, Moller-Larsen A *et al* 1995 Increased risk of multiple sclerosis after late Epstein–Barr virus infection: a historical prospective study. *Mult Scler* **1**: 73–77

Haahr S, Munch M, Christensen T *et al* 1997 Cluster of multiple sclerosis patients from a Danish community. *Lancet* **349**: 923

Haarr M 1963 Retinal periphlebitis in multiple sclerosis. *Acta Neurol Scand* **39 (Suppl 4)**: 270–272

Haase AT, Ventura P, Gibbs CJ, Tourtellotte WW 1981 Measles virus nucleotide sequences: detection by hybridization *in situ*. *Science* **212**: 672–675

Haase CG, Guggenmos J, Brehm U *et al* 2001 The fine specificity of the myelin oligodendrocyte glycoprotein autoantibody response in patients with multiple sclerosis and normal healthy controls. *J Neuroimmunol* **114**: 220–225

Haase CG, Schmidt S, Faustmann PM 2002 Frequencies of the G-protein beta3 subunit C825T polymorphism and the delta32 mutation of the chemokine receptor-5 in patients with multiple sclerosis. *Neurosci Lett* **330**: 293–295

Hachem S, Aguirre A, Vives V *et al* 2005 Spatial and temporal expression of S100B in cells of oligodendrocyte lineage. *Glia* **52**: 81–97

Hachinski VC, Potter P, Merskey H 1987 Leuko-araiosis. *Arch Neurol* **44**: 21–23

Hackett J, Swanson P, Leahy D *et al* 1996 Search for retrovirus in patients with multiple sclerosis. *Ann Neurol* **40**: 805–809

Hackstein H, Bitsch A, Bohnert A *et al* 2001 Analysis of interleukin-4 receptor alpha chain variants in multiple sclerosis. *J Neuroimmunol* **15**: 240–248

Hadden JW, Speafico F 1985 New strategies of immunotherapy. *Springer Semin Immunopathol* 8: 139–152

Hader WJ 1982 Prevalence of multiple sclerosis in Saskatoon. *Can Med Assoc J* **127**: 295–297

Hader WJ, Feasby TE, Noseworthy JH *et al* 1985 Multiple sclerosis in Canadian native people. *Neurology* **35 (Suppl 1)**: 300 (abstract)

Hader WJ, Rozdilsky B, Nair CP 1986 The concurrence of multiple sclerosis and amyotrophic lateral sclerosis. *Can J Neurol Sci* **13**: 66–69

Hader WJ, Elliot M, Ebers GC 1988 Epidemiology of multiple sclerosis in London and Middlesex County, Ontario, Canada. *Neurology* **38**: 617–621

Hader WJ, Irvine DG, Schiefer HB 1990 A cluster-focus of multiple sclerosis at Henribourg, Saskatchewan. *Can J Neurol Sci* **17**: 391–394

Hader WJ, Seland TP, Hader MB *et al* 1996 The occurrence of multiple sclerosis in the Hutterites of North America. *Can J Neurol Sci* **23**: 291–295

Hadjivassiliou M, Grunewald RA, Chattopadhyay AK *et al* 1998 Clinical, radiological, neurophysiological and neuropathological characteristics of gluten ataxia. *Lancet* **352**: 1582–1585

Hadjivassiliou M, Grunewald R, Sharrack B *et al* 2003 Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* **126**: 685–691

Haegert DG, Francis GS 1992 Contribution of a single DQ beta chain residue to multiple sclerosis in French Canadians. *Hum Immunol* **34**: 85–90

Haegert DG, Francis GS 1993 HLA-DQ polymorphisms do not explain HLA class II associations with multiple sclerosis in two Canadian patient groups. *Neurology* **43**: 1207–1210

Haegart DG, Michaud M, Schwab C, Francis GS 1990 Multiple sclerosis and HLA class II susceptibility and resistance genes. *J Neurosci Res* **26**: 66–73

Haegert DG, Muntoni DG, Murru MR *et al* 1993 HAL-DQA1 and -DQB1 associations with multiple sclerosis in Sardinia and French Canada: evidence for

immunogenetically distinct patient groups. *Neurology* **43**: 548–552
Haegert DG, Swift FV, Benedikz J 1996 Evidence for a complex role of HLA class II genotypes in susceptibility to multiple sclerosis in Iceland. *Neurology* **46**: 1107–1111
Hafer-Macko C, Hsieh ST, Li CY *et al* 1996 Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. *Ann Neurol* **40**: 635–644
Hafler DA, Buchsbaum M, Johnson D, Weiner HL 1985a Phenotypic and functional analysis of T cells cloned directly from the blood and cerebrospinal fluid of patients with multiple sclerosis. *Ann Neurol* **18**: 451–458
Hafler DA, Fox DA, Manning ME *et al* 1985b *In vivo* activated T lymphocytes in the peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *N Engl J Med* **312**: 1405–1411
Hafler DA, Fallis RJ, Dawson DM *et al* 1986 Immunologic responses of progressive multiple sclerosis patients treated with an anti-T-cell monoclonal antibody, anti-T12. *Neurology* **36**: 777–784
Hafler DA, Ritz F, Schlossman SF, Weiner HL 1988 Anti-CD4 and anti-CD2 monoclonal antibody infusions in subjects with multiple sclerosis: immunosuppressive effect and human anti-mouse responses. *J Immunol* **141**: 131–138
Hafler DA, Saadeh MG, Kuchroo VK *et al* 1996 TCR usage in human and experimental demyelinating disease. *Immunol Today* **17**: 152–159
Hageman ATH, Gabreels FJM, de Jong JGN *et al* 1995 Clinical symptoms of adult metachromatic leukodystrophy and arylsulfatase A pseudo deficiency. *Arch Neurol* **52**: 408–413
Haghighi S, Andersen O, Rosengren L *et al* 2000 Incidence of CSF abnormalities in siblings of multiple sclerosis patients and unrelated controls. *J Neurol* **247**: 616–622
Hahn CD, Shroff MM, Blaser SI, Banwell BL 2004 MRI criteria for multiple sclerosis. Evaluation in a pediatric cohort. *Neurology* **62**: 806–808
Hahn JS, Siegler DJ, Enzmann D 1996 Intravenous gammaglobulin therapy in recurrent acute disseminated encephalomyelitis. *Neurology* **46**: 1173–1174
Haile RW, Iselius L, Hodge S *et al* 1981 Segregation and linkage of 40 multiplex multiple sclerosis families. *Hum Heredity* **31**: 252–258
Hailman E, Burack WR, Shaw AS *et al* 2002 Immature $CD4^{+}CD8^{+}$ thymocytes form a multifocal immunological synapse with sustained tyrosine phosphorylation. *Immunity* **16**: 839–848
Haimanot R 1985 MS – a case report on an Ethiopian. *Ethiopian Med J* **23**: 27
Haines JL, Ter-Minassian M, Bazyk A *et al* 1996 A complete genomic screen for multiple sclerosis underscores a role for the major histocompatibility complex. *Nature Genet:* **13**: 469–471
Haines JL, Terwedow HA, Burgess K *et al* 1998 Linkage of the MHC to familial multiple sclerosis suggests genetic heterogeneity. The Multiple Sclerosis Genetics Group. *Hum Mol Genet* **7**: 1229–1234
Haines JL, Bradford Y, Garcia ME *et al* 2002 Multiple susceptibility loci for multiple sclerosis. *Hum Mol Genet* **11**: 2251–2256
Hajihosseini M, Tham TN, Dubois-Dalcq M 1996 Origin of oligodendrocytes within the human spinal cord. *J Neurosci* **16**: 7981–7994
Halawa I, Lolli F, Link H 1989 Terminal component of complement C9 in CSF and plasma of patients with MS and aseptic meningitis. *Acta Neurol Scand* **80**: 130–135
Hale G, Xia MQ, Tighe HP *et al* 1990 The Campath-1 antigen (CDw52). *Tissue Antigens* **35**: 1–10
Halfpenny CA, Scolding NJ 2003 Immune-modifying agents do not impair the survival, migration or proliferation of oligodendrocyte progenitors (CG-4) in vitro. *J Neuroimmunol* **139**: 9–16
Hall A, Giese NA, Richardson WD 1996 Spinal cord oligodendrocytes develop from ventrally derived progenitor cells that express PDGF alpha-receptors. *Development* **122**: 4085–4094
Hall GL, Compston DAS, Scolding NJ 1997a Beta-interferon and multiple sclerosis. *Trends Neurosci* **20**: 63–67
Hall GL, Wing MG, Compston DAS, Scolding NJ 1997b Beta-interferon regulates the immunoregulatory activity of neonatal rodent microglia. *J Neuroimmunol* **72**: 11–19
Hall GL, Girdlestone J, Compston DAS, Wing MG 1999 Recall antigen presentation by gamma interferon activated microglia results in T cell proliferation, cytokine release and propagation of the immune response. *J Neuroimmunol* **98**: 105–111
Hall JI 1967 Studies on demyelinated peripheral nerves in guinea-pigs with experimental allergic neuritis: a histological and electrophysiological study. II Electrophysiological observations. *Brain* **90**: 313–332
Hall M 1841 *On Diseases and Derangements of the Nervous System in their Primary Forms and in their Modifications by Age, Sex, Constitution, Hereditary Predisposition, Excesses, General Disorder and Organic Disease*. London: Ballière
Hall SM, Redford EJ, Smith KJ 2000 Tumour necrosis factor-alpha has few morphological effects within the dorsal columns of the spinal cord, in contrast to its effects in the peripheral nervous system. *J Neuroimmunol* **106**: 130–136
Haller P, Patzold U 1979 Die Optikusneuritis im Kindersalter. *Forschr Neurol Psychiatr* **47**: 209–216
Hallervorden J 1940 Die zentralen Entmarkungserkrankungen. *Dtsch Z Nervenheilk* **150**: 201–239
Hallervorden J, Spatz H 1933 Über die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprozessen. *Arch Psychiatr Nervenkr* **98**: 641–701
Hallet M, Londsey JW, Adelstein BD, Riley PO 1985 Controlled trial of isoniazid therapy for severe postural cerebellar tremor in multiple sclerosis. *Neurology* **35**: 1374–1377
Halliday AM 1993 The visual evoked potential in the investigation of diseases of the optic nerve. In: Halliday AM (ed.) *Evoked Potentials in Clinical Testing*. Edinburgh: Churchill Livingstone, pp. 195–278
Halliday AM, Wakefield GS 1963 Cerebral evoked potentials in patients with associated sensory loss. *J Neurol Neurosurg Psychiatry* **26**: 211–219
Halliday AM, McDonald WI, Mushin J 1972 Delayed visual evoked response in optic neuritis. *Lancet* **i**: 982–985
Halliday AM, McDonald WI, Mushin J 1973a Visual evoked response in diagnosis of multiple sclerosis. *Br Med J* **4**: 661–664
Halliday AM, McDonald WI, Mushin J 1973b Delayed pattern-evoked responses in optic neuritis in relation to visual acuity. *Trans Ophthalmol Soc UK* **93**: 315–324
Halliday AM, Halliday E, Kriss A *et al* 1976 The pattern-evoked potential in compression of the anterior visual pathways. *Brain* **99**: 357–374
Hallpike JF, Adams CW, Bayliss OB 1970a Histochemistry of myelin: proteolytic activity around multiple sclerosis plaques. *Histochem J* **2**: 199–208
Hallpike JF, Adams CW, Bayliss OB 1970b Histochemistry of myelin: loss of basic protein in early myelin breakdown and multiple sclerosis plaques. *Histochem J* **2**: 323–328
Hamdi T 1975 Multiple sclerosis in Iraq: a clinical and geomedical survey. *J Postgrad Med* **21**: 1–9
Hamidon BB, Raymond AA 2003 Acute disseminated encephalomyelitis (ADEM) presenting as seizures secondary to anti-tetanus toxin vaccination. *Med J Malaysia* **58**: 780–782
Hammarberg H, Lidman O, Lundberg H *et al* 2000 Neuroprotection by encephalomyelitis: rescue of mechanically injured neurons and neurotrophin production by CNS-infiltrating T and natural killer cells. *J Neurosci* **20**: 5283–5291
Hammarstrom AKM, Gage PW 1998 Inhibition of oxidative metabolism increases persistent sodium current in rat CA1 hippocampal neurons. *J Physiol* **510**: 735–741
Hammarstrom AKM, Gage PW 1999 Nitric oxide increases persistent sodium current in rat hippocampal neurons. *J Physiology* **520**: 451–461
Hammond SR, De Wytt C, Maxwell IC *et al* 1987 The epidemiology of multiple sclerosis in Queensland, Australia. *J Neurol Sci* **80**: 185–204
Hammond SR, English D, de Wytt C *et al* 1988a The clinical profile of MS in Australia: a comparison between medium- and high-frequency prevalence zones. *Neurology* **38**: 980–986

Hammond SR, McLeod JG, Millingen KS *et al* 1988b The epidemiology of multiple sclerosis in 3 Australian cities: Perth, Newcastle and Hobart. *Brain* **111**: 1–25

Hammond SR, McLeod JG, Macaskill P, English D 1996 Multiple sclerosis in Australia: socio-economic factors. *J Neurol Neurosurg Psychiatry* **61**: 311–313

Hammond SR, English DR, McLeod JG 2000a The age-range of risk of developing multiple sclerosis: evidence from a migrant population in Australia. *Brain* **123**: 968–974

Hammond SR, McLeod JG, Macaskill P, English DR 2000b Multiple sclerosis in Australia: prognostic factors. *J Clin Neurosci* **7**: 16–19

Hammond WA 1871 *A Treatise on Diseases of the Nervous System*. New York: Appleton, pp. 278–300

Hammondeh M, Kahn MA 1982 Clinical variant of systemic lupus erythematosus resembling multiple sclerosis. *J Rheumatol* **9**: 336–337

Hanahan D 1999 Peripheral-antigen-expressing cells in thymic medulla: factors in self-tolerance and autoimmunity. *Curr Opin Immunol* **10**: 656–662

Handa R, Sahota P, Kumar M *et al* 2003 In vivo proton magnetic resonance spectroscopy (MRS) and single photon emission computerized tomography (SPECT) in systemic lupus erythematosus (SLE). *Magn Reson Med* **21**: 1033–1037

Hanefeld F, Bauer HJ, Christen HJ *et al* 1991 Multiple sclerosis in childhood: report of 15 cases. *Brain Dev* **13**: 410–416

Hanrahan PS, Russel AS, McLean DR 1988 Ankylosing spondylitis and multiple sclerosis: a possible association. *J Rheumatol* **15**: 1512–1514

Hansen C, Hopf HC, Treede RD 1996 Paradoxical heat sensation in patients with multiple sclerosis: evidence for a supraspinal integration of temperature sensation. *Brain* **119**: 1729–1736

Hao Q, Saida T, Kawakami H *et al* 1992 HLAs and genes in Japanese patients with multiple sclerosis: evidence for increased frequencies of HLA-Cw3, HLA-DR2 and HLA-DQB1*0602. *Hum Immunol* **35**: 116–124

Hao Q, Miyashita N, Matsui M *et al* 2002 *Chlamydia pneumoniae* infection associated with enhanced MRI spinal lesions in multiple sclerosis. *Mult Scler* **8**: 436–440

Haran MJ, Jenney AW, Keenan RJ *et al* 2001 Paraplegia secondary to *Burkholderia pseudomallei* myelitis: a case report. *Arch Phys Med Rehabil* **82**: 1630–1632

Harbison JW, Calabrese VP, Edlich RF 1989 A fatal case of sun exposure in a multiple sclerosis patient. *J Emerg Med* **7**: 465–467

Harbo HF, Celius EG, Vardtdal F, Spurkland A 1999 CTLA4 promoter and exon 1 dimorphisms in multiple sclerosis. *Tissue Antigens* **53**: 106–110

Harbo HF, Datta P, Oturai A *et al* 2003 Two genome-wide linkage disequilibrium screens in Scandinavian multiple sclerosis patients. *J Neuroimmunol* **143**: 101–106

Harbo HF, Lie BA, Sawcer S *et al* 2004 Genes in the HLA class I region may contribute to the HLA class II-associated genetic susceptibility to multiple sclerosis. *Tissue Antigens* **63**: 237–247

Hardesty I 1904 On the development and nature of the neuroglia. *Am J Anat* **3**: 229–268

Harding AE 1984 *The Hereditary Ataxias and Related Disorders*. Edinburgh: Churchill Livingstone

Harding AE, Sweeney MG, Miller DH *et al* 1992 Occurrence of a multiple sclerosis-like illness in women who have a Leber's hereditary optic neuropathy mitochondrial DNA mutation. *Brain* **115**: 979–989

Hardy RJ, Friedrich VL 1996 Oligodendrocyte progenitors are generated throughout the embryonic mouse brain, but differentiate in restricted foci. *Development* **122**: 2059–2069

Hargreaves ER 1969 Epidemiological studies in Cornwall. *Proc R Soc Med* **54**: 209–216

Haring JS, Perlman S 2003 Bystander CD4 T cells do not mediate demyelination in mice infected with a neurotropic coronavirus. *J Neuroimmunol* **137**: 42–50

Haring JS, Pewe LL, Perlman S 2002 Bystander CD8 T cell-mediated demyelination after viral infection of the central nervous system. *J Immunol* **169**: 1550–1555

Harris JO, Frank JA, Patronas N *et al* 1991 Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing–remitting multiple sclerosis: implications for clinical trials and natural history. *Ann Neurol* **29**: 548–555

Harris W 1940 An analysis of 1,433 cases of paroxysmal trigeminal neuralgia (trigeminal tic) and the end results of Gasserian alcohol injection. *Brain* **63**: 209–224

Harris W 1950 Rare forms of paroxysmal trigeminal neuralgia and their relation to disseminated sclerosis. *Br Med J* **2**: 1015–1019

Harrison AC, Becker WJ, Stell WK 1987 Colour vision abnormalities in multiple sclerosis. *Can J Neurol Sci* **14**: 279–285

Harrison BM, McDonald WI, Ochoa J 1972 Remyelination in the central diphtheria toxin lesion. *J Neurol Sci* **17**: 293–302

Hart MN, Earle KM 1975 Haemorrhagic and perivenous encephalitis: a clinical-pathological review of 38 cases. *J Neurol Neurosurg Psychiatry* **38**: 585–591

Hartelius L, Runmarker B, Andersen O 2000 Prevalence and characteristics of dysarthria in a multiple-sclerosis incidence cohort: relation to neurological data. *Folia Phoniatr Logop* **52**: 160–177

Hartmann M, Rottach KG, Wohlgemuth WA, Pfadenhauer K 1999 Trigeminal neuralgia triggered by auditory stimuli in multiple sclerosis. *Arch Neurol* **56**: 731–733

Hartung HP, Grossman RI 2001 ADEM: distinct disease or part of the MS spectrum? *Neurology* **56**: 1257–1260

Hartung HP, Kieseier BC 2000 The role of matrix metalloproteinases in autoimmune damage to the central and peripheral nervous system. *J Neuroimmunol* **107**: 140–147

Hartung HP, Munschauer FE 2004 Assessment and management of neutralizing antibodies in patients with multiple sclerosis. *J Neurol* **251**: II40–II42

Hartung HP, Gonsette R, Konig N *et al* 2002 Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* **360**: 2018–2025

Hartung HP, Schellekens H, Munschauer III F 2004 Neutralizing antibodies to interferon beta patients with multiple sclerosis: scientific background and clinical implications. *J Neurol* **251**: II1–II3

van Haver H, Lissoir F, Droissart C *et al* 1986 Transfer factor therapy in multiple sclerosis: a three year prospective double-blind clinical trial. *Neurology* **36**: 1399–1402

Harzheim M, Schlegel U, Urbach H *et al* 2004 Discriminatory features of acute transverse myelitis: a retrospective analysis of 45 patients. *J Neurol Sci* **217**: 217–223

Hashimoto LL, Mak T, Ebers GC 1992 T-cell receptor alpha-chain polymorphisms in multiple sclerosis. *J Neuroimmunol* **40**: 41–48

Hashimoto LL, Walter M, Cox D, Ebers GC 1993 Immunoglobulin heavy chain variable region polymorphisms in multiple sclerosis susceptibility. *J Neuroimmunol* **44**: 77–83

Haskell CA, Hancock WW, Salant DJ *et al* 2001 Targeted deletion of CX(3)CR1 reveals a role for fractalkine in cardiac allograft rejection. *J Clin Invest* **108**: 679–688

Hassler R, Bronisch F, Mandringer F, Riechert T 1975 Intention myoclonus of multiple sclerosis, its patho-anatomical basis and stereotaxic relief. *Neurochirurgica* **18**: 90–106

Hasson J, Terry RD, Zimmermann HM 1958 Peripheral neuropathy in multiple sclerosis. *Neurology* **8**: 503–510

Hatten ME, Liem, RKH, Mason CA 1991 Astroglia in CNS injury. *Glia* **4**: 233–243

Hauben E, Butovsky O, Nevo U *et al* 2000a Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. *J Neurosci* **20**: 6421–6430

Hauben E, Nevo U, Yoles E *et al* 2000b Autoimmune T cells as potential neuroprotective therapy for spinal cord injury. *Lancet* **354**: 286–287

Hauben E, Agranov E, Gothilf A *et al* 2001 Posttraumatic therapeutic vaccination with modified myelin self antigen prevents complete paralysis while avoiding autoimmune disease. *J Clin Invest* **108**: 591–599

Haupts M, Schejbal P, Pohlau D, Malin J, Przuntek H, Gehlen W 1994 Epidemiological data on multiple sclerosis from an industrial area in north-west Germany. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 143–146

Hauser ER, Boehnke M, Guo SW, Risch N 1996 Affected-sib-pair interval mapping and exclusion for complex genetic traits: sampling considerations. *Genet Epidemiol* **13**: 117–137

Hauser SL, Bresnan MJ, Reinherz EL, Weiner HL 1982 Childhood multiple sclerosis: clinical features and demonstration of changes in T cell subsets with disease activity. *Ann Neurol* **11**: 463–468

Hauser SL, Dawson DM, Lehrich JR *et al* 1983 Intensive immunosuppression in progressive multiple sclerosis. *N Engl J Med* **308**: 173–180

Hauser SL, Aubert C, Burks JS *et al* 1986 Analysis of human T-lymphotropic virus sequences in multiple sclerosis tissue. *Nature* **322**: 176–177

Hauser SL, Fleischnick E, Weiner HL *et al* 1989 Extended major histocompatibility complex haploptypes in patients with multiple sclerosis. *Neurology* **39**: 275–277

Hauser SL, Doolittle TH, Lincoln R, Brown RH, Dinarello CA 1990 Cytokine accumulations in CSF of multiple sclerosis patients: frequent detection of interleukin-1 and tumor necrosis factor but not interleukin-6. *Neurology* **40**: 1735–1739

Hauser SL, Doolittle TH, Lopez-Bresnahan M *et al* 1992 Antispasticity effect of threonine in multiple sclerosis. *Arch Neurol* **49**: 923–926

Hauser SL, Oksenberg JR, Lincoln R *et al* 2000 Interaction between HLA-DR2 and abnormal brain MRI in optic neuritis and early MS. Optic Neuritis Study Group. *Neurology* **54**: 1859–1861

van Haver H, Lissoir F, Droissart C *et al* 1986 Transfer factor therapy in multiple sclerosis: a three year prospective double-blind clinical trial. *Neurology* **36**: 1399–1402

Hawkes CH 2002 Is multiple sclerosis a sexually transmitted infection? *J Neurol Neurosurg Psych* **73**: 439–443

Hawkins CP, Munro PMG, MacKenzie F *et al* 1990a Duration and selectivity of blood-brain barrier breakdown in chronic relapsing experimental allergic encephalomyelitis studied using gadolinium-DTPA and protein markers. *Brain* **113**: 365–378

Hawkins CP, MacKenzie F, Tofts PS *et al* 1990b Patterns of blood-brain barrier breakdown in inflammatory demyelination. *Brain* **114**: 801–810

Hawkins SA, Kee F 1988 Updated epidemiological studies of multiple sclerosis in Northern Ireland. *J Neurol* **235 (Suppl)**: S86

Hawkins SA, McDonnell GV 1999 Benign multiple sclerosis? Cliical course, long term follow up, and asessement of prognostic factors. *J Neurol Neurosurg Psych* **67**: 148–152

Hawley RJ 2000 Hyperammonia possibly due to corticosteroids. *Arch Neurol* **57**: 1085–1086

Hayashi T, Morimoto C, Burks JS *et al* 1988 Dual-labeled immunocytochemistry of the active multiple sclerosis lesion: major histocompatibility complex and activation antigens. *Ann Neurol* **24**: 523–531

Hayday AC 2000 γδ T cells: a right time and a right place for a conserved third way of protection. *Annu Rev Immunol* **18**: 975–1026

Hayes CE, Nashold FE, Spach KM, Pedersen LB 2003 The immunological functions of the vitamin D endocrine system. *Mol Cell Biol* **49**: 277–300

He B, Navikas V, Lundahl J *et al* 1995 Tumor necrosis factor α-308 alleles in multiple sclerosis and optic neuritis. *J Neuroimmunol* **63**: 143–147

He B, Xu C, Yang B *et al* 1998 Linkage and association analysis of genes encoding cytokines and myelin proteins in multiple sclerosis. *J Neuroimmunol* **86**: 13–19

He B, Giedraitis V, Ligers A *et al* 2002a Sharing of a conserved haplotype suggests a susceptibility gene for multiple sclerosis at chromosome 17p11. *Eur J Hum Genet* **10**: 271–275

He B, Wen W, Strong MJ 2002b Activated microglia (BV-2) facilitation of TNF-α-mediated motor neuron death in vitro. *J Neuroimmunol* **128**: 31–38

He W, Ingraham C, Rising L *et al* 2001 Multipotent stem cells from the mouse basal forebrain contribute GABAergic neurons and oligodendrocytes to the cerebral cortex during embryogenesis. *J Neurosci* **21**: 8854–8862

Heales SJR, Barker JE, Stewart VC *et al* 1997 Nitric oxide, energy metabolism and neurological disease. *Biochem Soc Trans* **25**: 939–943

Heard RN, McDonald WI, Batchelor JR *et al* 1989a An RFLP study of HLA-D gene polymorphism in multiple sclerosis. *Immunobiology of HLA* **1**: 913–915

Heard RN, Cullen C, Middleton D *et al* 1989b An allelic cluster of DQ alpha restriction fragments is associated with multiple sclerosis: evidence that a second haplotype may influence disease susceptibility. *Hum Immunol* **25**: 111–123

Heath WR, Miller JFAP 1993 Expression of two α chains on the surface of T cells in T cell receptor transgenic mice. *J Exp Med* **178**: 1807–1811

Heaton RK, Nelson LM, Thompson DS *et al* GM 1985 Neuropsychological findings in relapsing–remitting and chronic-progressive multiple sclerosis. *J Consult Clin Psychol* **53**: 103–110

Heber-Katz E, Acha-Orbea H 1989 The V-region disease hypothesis: evidence from autoimmune encephalomyelitis. *Immunol Today* **10**: 164–169

Hedera P, Fink KJ, Bockenstedt PL, Brewer GJ 2003 Myeloneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin. *Arch Neurol* **60**: 1303–1306

Hedlund G, Sandberg-Wollheim M, Sjögren HO 1989 Increased proportion of $CD4^+CDw29^+CD45R^-UCHL\text{-}1^+$ lymphocytes in the cerebrospinal fluid of both multiple sclerosis patients and healthy individuals. *Cell Immunol* **118**: 406–412

Heesen C, Kolbeck J, Gold SM *et al* 2003 Delivering the diagnosis of MS – results of a survey among patients and neurologists. *Acta Neurol Scand* **107**: 363–368

Heggarty S, Sawcer SJ, Hawkins S *et al* 2003 A genome wide scan for association with multiple sclerosis in a N. Irish case control population. *J Neuroimmunol* **143**: 93–96

Hein T, Hopfenmuller W 2000 Projection of the number of multiple sclerosis patients in Germany. *Nervenartz* **71**: 288–294

Heininger K, Fierz W, Schafer B *et al* 1989 Electrophysiological investigations in adoptively transferred experimental autoimmune encephalomyelitis in the Lewis rat. *Brain* **112**: 537–552

Heinrich M, Gorath M, Richter-Landsberg C 1999 Neurotrophin-3 (NT-1) modulates early differentiation of oligodendrocytes in rat brain cortical cultures. *Glia* **28**: 244–255

Heins N, Malatesta P, Cecconi F *et al* 2002 Glial cells generate neurons: the role of the transcription factor Pax6. *Nature Neurosci* **5**: 308–315

Heinzlef O, Alamowitch S, Sazdovitch V *et al* 1999 Autoimmune disease in families of French patients with multiple sclerosis. *Acta Neurol Scand* **100**: 1–5

Heinzlef O, Weill B, Johanet C *et al* 2002 Anticardiolipin antibodies in patients with multiple sclerosis do not represent a subgroup of patients according to clinical, familial, and biological characteristics. *J Neurol Neurosurg Psychiatry* **72**: 647–649

Heltberg A 1987 Twin studies in multiple sclerosis. *Ital J Neurol Sci* **6**: 35–39

Heltberg A, Holm NV 1982 Concordance in twins and recurrence in sibships in multiple sclerosis. *Lancet* **i**: 1068

Hely MA, McManus PG, Doran TJ *et al* 1986a Acute optic neuritis: a prospective study of risk factors for multiple sclerosis. *J Neurol Neurosurg Psychiatry* **49**: 1125–1130

Hely MA, McManus PG, Walsh JC, McLeod JG 1986b Visual evoked responses and ophthalmological examination in optic neuritis: a follow-up study. *J Neurol Sci* **75**: 275–283

Hemmer B, Gran B, Zhao Y *et al* 1999 Identification of candidate T cell epitopes and molecular mimics in chronic Lyme disease. *Nature Med* **5**: 1346–1349

Hench PS 1938 The ameliorating effect of pregnancy on chronic atrophic (infectious rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis. *Proc Staff Meet Mayo Clin* **13**: 161–167

Henderson RD, Bain CJ, Pender MP 2000 The occurrence of autoimmune diseases in patients with multiple sclerosis and their families. *J Clin Neurosci* **7**: 434–437

Henke AF, Cohle SD, Cottingham SL 2000 Fatal hyperthermia secondary to sunbathing in a patient with multiple sclerosis. *Am J Forensic Med Pathol* **21**: 204–206

Hennessey A, Swingler RJ, Compston DAS 1989 The incidence and mortality of multiple sclerosis in South East Wales. *J Neurol Neurosurg Psychiatry* **52**: 1085–1089

Hennessey A, Robertson NP, Swingler R, Compston DAS 1999 Urinary, faecal and sexual dysfunction in patients with multiple sclerosis. *J Neurol* **246**: 1027–1032

Hensiek AE, Sawcer SJ, Feakes R *et al* 2002 HLA-DR 15 is associated with female gender and younger age at diagnosis in multiple sclerosis. *J Neurol Neurosurg Psych* **72**: 184–187

Hensiek AE, Roxburgh R, Smilie B *et al* 2003a Updated results of the United Kingdom linkage based genome screen in multiple sclerosis. *J Neuroimmunol* **143**: 25–30

Hensiek AE, Roxburgh R, Meranian M *et al* 2003b Osteopontin gene and clinical severity of multiple sclerosis. *J Neurol* **250**: 943–947

Hensiek AE, Seaman S, Barcellos L *et al* 2005 Familial effects on the clinical course in multiple sclerosis (submitted)

Henson RA, Urich H 1982 *Cancer and the Nervous System: The Neurological Manifestations of Systemic Malignant Disease*. Oxford: Blackwell Scientific Publications

Herishanu Y, Louzoun Z 1986 Trihexyphenidyl treatment of vertical pendular nystagmus. *Neurology* **36**: 82–84

Herishanu YO, Badarna S, Sarov B *et al* 1989 A possible harmful late effect of methylprednisolone therapy on a time cluster of optic neuritis. *Acta Neurol Scand* **80**: 163–170, 569–574

Herman A, Kappler JW, Marrack P, Pullen AM 1991 Superantigens: mechanisms of T cell stimulation and role in immune responses. *Annu Rev Immunol* **9**: 745–772

Hermans G, Stinissen P, Hauben L *et al* 1997 Cytokine profile of myelin basic protein reactive T cells in multiple sclerosis and healthy individuals. *Ann Neurol* **42**: 18–27

Hermanson O, Jepsen K, Rosenfeld M 2002 N-CoR controls differentiation of neural stem cells into astrocytes. *Nature* **419**: 934–939

Hernán MA, Olek MJ, Ascherio A 1999 Geographic variation of MS incidence in two prospective studies of US women. *Neurology* **53**: 1711–1718

Hernán MA, Zhang SM, Lipworth L *et al* 2001 Multiple sclerosis and age at infection with common viruses. *Epidemiology* **12**: 301–306

Hernán MA, Jick SS, Olek MJ, Jick H 2004 Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology* **63**: 838–842

Hernán MA, Jick SS, Logroscino G *et al* 2005 Cigarette smoking and the progression of multiple sclerosis. *Brain* **128**: 1461–1465

Hernandez MA 2002 Epidemiology of multiple sclerosis in the Canary Islands (Spain): a study on the island of La Palma. *J Neurol* **249**: 1378–1381

Herndon RM, Brooks B 1985 Misdiagnosis of multiple sclerosis. *Semin Neurol* **5**: 94–98

Herndon RM, Rubinstein LJ, Freeman JM, Mathieson G 1970 Light and electron microscopic observations on Rosenthal fibers in Alexander's disease and in multiple sclerosis. *J Neuropathol Exp Neurol* **29**: 524–551

Herrera DG, Garcia-Verdugo JM, Alvarez-Buylla A 1999 Adult-derived neural precursors transplanted into multiple regions in the adult brain. *Ann Neurol* **46**: 867–877

Herrnstadt C, Elson JL, Fahy E *et al* 2002 Reduced-median-network analysis of complete mitochondrial DNA coding-region sequences for the major African, Asian, and European haplogroups. *Am J Hum Genet* **70**: 1152–1171

Herroelen L, de Keyser J, Eginger G 1991 Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine. *Lancet* **338**: 1174–1175

Hess CW, Mills KR, Murray NMF 1986 Measurement of central motor conduction in multiple sclerosis by magnetic brain stimulation. *Lancet* **ii**: 355–358

Hess CW, Mills KR, Murray NMF, Schriefer TN 1987 Magnetic brain stimulation: central motor conduction studies in multiple sclerosis. *Ann Neurol* **22**: 744–752

Heun R, Sliwka U, Ruttinger H, Schimrigk 1992 Intrathecal versus systemic corticosteroids in the treatment of multiple sclerosis: results of a pilot study. *J Neurol* **239**: 31–35

Heyer E 1995 Mitochondrial and nuclear genetic contribution of female founders to a contemporary population in northeast Quebec. *Am J Hum Genet* **56**: 1450–1455

Heyes MP, Achim CL, Wiley CA *et al* 1996 Human microglia convert l-tryptophan into the neurotoxin quinolinic acid. *Biochem J* **320**: 595–597

Hickey WF 1991 Migration of hematogenous cells through the blood brain barrier and the initiation of CNS inflammation. *Brain Pathol* **1**: 97–105

Hickey WF 2001 Basic principles of immunological surveillance of the normal central nervous system. *Glia* **36**: 118–124

Hickey WF, Gonatas NK 1984 Suppressor T-lymphocytes in the spinal cord of Lewis rats recovered from acute experimental allergic encephalomyelitis. *Cell Immunol* **85**: 284–288

Hickey WF, Kimura H 1988 Perivascular microglial cells of the CNS are bone-marrow derived and present antigen *in vivo*. *Science* **239**: 290–293

Hickey WF, Osborn JP, Kirby WM 1985 Expression of Ia molecules by astrocytes during acute experimental allergic encephalomyelitis in the Lewis rat. *Cell Immunol* **91**: 528–535

Hickey WF, Hsu BL, Kimura H 1991 T-lymphocyte entry into the central nervous system. *J Neurosci Res* **28**: 254–260

Hickey WF, Vass K, Lassmann H 1992 Bone marrow-derived elements in the central nervous system: an immunohistochemical and ultrastructural survey of rat chimeras. *J Neuropathol Exp Neurol* **51**: 246–256

Hickman SJ, Brex PA, Brierley CMH *et al* 2001 Detection of optic nerve atrophy following a single episode of unilateral optic neuritis by MRI using a fat-saturated short-echo fast FLAIR sequence. *Neuroradiology* **43**: 123–128

Hickman SJ, Brierley CM, Brex PA *et al* 2002a Continuing optic nerve atrophy following optic neuritis: a serial MRI study. *Mult Scler* **8**: 339–342

Hickman SJ, Dalton CM, Miller DH, Plant GT 2002b Management of acute optic neuritis. *Lancet* **360**: 1953–1962

Hickman SJ, Kapoor R, Jones SJ *et al* 2003 Corticosteroids do not prevent optic nerve atrophy following optic neuritis. *J Neurol Neurosurg Psychiatry* **74**: 1139–1141

Hickman SJ, Toosy AT, Miszkiel KA *et al* 2004a Visual recovery following acute optic neuritis: a clinical, electrophysiological and magnetic resonance imaging study. *J Neurol* **251**: 996–1005

Hickman SJ, Toosy AT, Jones SJ *et al* 2004b A serial MRI study following optic nerve mean area in acute optic neuritis. *Brain* **127**: 2498–2505

Hickman SJ, Toosy AT, Jones SJ *et al* 2004c Serial magnetization transfer imaging in acute optic neuritis. *Brain* **127**: 692–700

Hierons R, Lyle TK 1959 Bilateral retrobulbar neuritis. *Brain* **82**: 56–67

Hietaharju A, Peltola J, Seppa J *et al* 2001 The coexistence of systemic lupus erythematosus and multiple sclerosis in a mother and daughter. *Scand J Rheumatol* **30**: 120–122

Higgins PJ, Weiner HL 1988 Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein and its fragments. *J Immunol* **140**: 440–445

Hill AB 1952 Assessment of therapeutic trials. *Trans Med Soc* **68**: 128–147

Hill KE, Zollinger LV, Watt HE *et al* 2004 Inducible nitric oxide synthase in chronic active multiple sclerosis plaques: distribution, cellular expression and association with myelin damage. *J Neuroimmunol* **151**: 171–179

Hillary FG, Chiaravalloti ND, Ricker JH *et al* 2003 An investigation of working memory rehearsal in multiple sclerosis using fMRI. *J Clin Exp Neuropsychol* **25**: 965–978

Hille B 1992 *Ionic Channels of Excitable Membranes*, 2nd edn. Sunderland, MA: Sinauer Associates

Hillert J 1993 Immunoglobulin constant region gene polymorphisms in multiple sclerosis. *J Neuroimmunol* **43**: 9–14

Hillert J 1994 Human leucocyte antigen studies in multiple sclerosis. *Ann Neurol* **36 (Suppl)**: S15–S17

Hillert J, Olerup O 1993 Multiple sclerosis is associated with genes within or close to the HLA-DR-DQ sub-region on a normal DR15 DQ6, Dw2 haplotype. *Neurology* **43**: 163–168

Hillert J, Leng C, Olerup O 1991 No association with germline T cell receptor beta chain alleles or haplotypes in Swedish patients with multiple sclerosis. *J Neuroimmunol* **31**: 141–147

Hillert J, Gronnig M, Nyland H *et al* 1992a Immunogenetic heterogeneity in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **55**: 887–890

Hillert J, Leng C, Olerup O 1992b T-cell receptor alpha-chain gene germline polymorphisms in multiple sclerosis. *Neurology* **42**: 80–84

Hillert J, Kall T, Vrethem M *et al* 1994 The HLA-Dw2 haplotype segregates closely with multiple sclerosis in multiplex families. *J Neuroimmunol* **50**: 95–100

Hilliard B, Samoilova EB, Liu TS *et al* 1999 Experimental autoimmune encephalomyelitis in NF-kappa B-deficient mice: roles of NF-kappa B in the activation and differentiation of autoreactive T cells. *J Immunol* **163**: 2937–2943

Hilton AA, Slavin AJ, Hilton DJ, Barnard CCA 1995 Characterisation of cDNA and genomic clones encoding human myelin oligodendrocyte glycoprotein. *J Neurochem* **65**: 309–318

Hilton J 1876 *On Rest and Pain. A course of lectures on the influence of mechanical and physiological rest in the treatment of accidents and surgical diseases and the diagnostic value of pain.* London: Bell & Sons

Hilton P, Hertogs, Stanton SL 1983 The use of desmopressin (DDAVP) for nocturia in women with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **46**: 854–855

Hindley DT, Newton RW, Clarke MA *et al* 1993 Steroid-responsive relapsing encephalopathy presenting in young children. *Neuropediatrics* **24**: 182

Hinds J, Eidelman B, Wald A 1990 Prevalence of bowel dysfunction in multiple sclerosis. *Gastroenterology* **98**: 1538–1542

Hinks GL, Franklin RJ 2000 Delayed changes in growth factor gene expression during slow remyelination in the CNS of aged rats. *Mol Cell Neurosci* **16**: 542–556

Hinks LJ, Price SE, Mason CR *et al* 1995 Single strand conformation analysis of two genes within the first intron of the neurofibromatosis type I gene in patients with multiple sclerosis. *Neuropathol Appl Neurobiol* **21**: 201–207

Hinrichs DJ, Humphres RC 1983 The response of the nude (athymic) rat to actively induced and transferred experimental allergic encephalomyelitis. *J Immunol* **131**: 4–5

Hirschberg DL, Schwartz M 1995 Macrophage recruitment to acutely injured central nervous system is inhibited by a resident factor: a basis for an immune-brain barrier. *J Neuroimmunol* **61**: 89–96

Hirschbiegel H 1967 Remittierende Verlaüfe bei Spinaltumoren. *Dtsch Z Nervenheilk* **190**: 74–82

Hisahara S, Shoji S, Okano H, Miura M 1997 ICE-CED-3 family executes oligodendrocyte apoptosis by tumor necrosis factor. *J Neurochem* **69**: 10–20

Hjalgrim H, Rasmussen S, Rostgaard K *et al* 2004 Familial clustering of Hodgkin lymphoma and multiple sclerosis. *J Ntal Cancer Inst* **96**: 780–784

Hjelmström P, Juedes AE, Fjell J, Ruddle NH 1998a B cell deficient mice develop experimental allergic encephalomyelitis with demyelination after myelin oligodendrocyte glycoprotein immunization. *J Immunol* **161**: 4480–4483

Hjelmström P, Juedes AE, Ruddle NH 1988b Cytokines and antibodies in myelin oligodendrocyte glycoprotein-induced experimental allergic encephalomyelitis. *Res Immunol* **149:** 794–804; 847–848; 855–860

Hjorth RJ, Willison RG 1973 The electromyogram in facial myokymia and hemifacial spasm. *J Neurol Sci* **20**: 117–126

Ho H-Z, Tiwari JL, Haile RW, Terasaki PI, Morton NE 1982 HLA-linked and unlinked determinants of multiple sclerosis. *Immunogenetics* **15**: 509–517

Ho KL, Wolfe DE 1981 Concurrence of multiple sclerosis and primary intracranial neoplasms. *Cancer* **47**: 2913–2919

Hobart JC 2002 Measuring disease impact in disabling neurological conditions: are patients' perspectives and scientific rigor compatible? *Curr Opin Neurol* **15**: 721–724

Hobart JC, Thompson AJ 2002 Measurement of neurological outcomes. In: Asbury AK, McKhann G, McDonald WI *et al* (eds) *Diseases of the Nervous System*, 3rd edn, 2 vols. Cambridge: Cambridge University Press, pp. 105–117

Hobart JC, Lamping DL, Thompson AJ 1996 Evaluating neurological outcome measures: the bare essentials. *J Neurol Neurosurg Psychiatry* **60**: 127–130

Hobart JC, Freeman JA, Thompson AJ 2000 Kurtzke scales revisited: the application of psychometric methods to clinical intuition. *Brain* **123**: 1027–1040

Hobart JC, Lamping D, Fitzpatrick R *et al* 2001 The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain* **124**: 962–973

Hobart JC, Riazi A, Lampling DL *et al* 2003 Measuring the impact of MS on walking ability: the 12-item MS Walking Scale (MSWS-12). *Neurology* **60**: 31–36

Hochberg MC 1997 Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* **40**: 1725

Hockertz MK, Paty DW, Beall SS 1998 Susceptibility to relapsing progressive multiple sclerosis is associated with inheritance of a gene linked to the variable region of the TcR beta chain locus: use of affected family-based controls. *Am J Hum Genet* **62**: 373–385

Hoefsmit ECM, Duijvestijn AM, Kamperdijk EWA 1982 Relation between Langerhans cells, veiled cells, and interdigitating cells. *Immunobiology* **161**: 255–265

Hoek RM, Ruuls SR, Murphy CA *et al* 2000 Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science* **290**: 1768–1771

Hofbauer M, Wiesener S, Babbe H *et al* 2003 Clonal tracking of autoaggressive T cells in polymyositis by combining laser microdissection, single-cell PCR, and CDR3- spectratype analysis. *Proc Natl Acad Sci USA* **100**: 4090–4095

Hoffman HI 1955 Acute necrotic myelopathy. *Brain* **78**: 377–393

Hoffman RE, Zack MM, Davis LE, Burchfiel CM 1981 Increased incidence and prevalence of multiple sclerosis in Los Alamos County, New Mexico. *Neurology* **31**: 1489–1492

Hoffmann JA, Kafatos FC, Janeway CA, Ezekowitz RAB 1999 Phylogenetic perspectives in innate immunity. *Science* **284**: 1313–1318

Hoffmann V, Pohlau D, Przuntek H *et al* 2002 A null mutation within the ciliary neurotrophic factor (CNTF) gene: implications for susceptibility and disease severity in patients with multiple sclerosis. *Genes Immun* **3**: 53–55

Hofman FM, Hinton DR, Johnson K, Merrill JE 1989 Tumour necrosis factor identified in multiple sclerosis brain. *J Exp Med* **170**: 607–612

Höfteberger R, Aboul-Enein F, Brueck W *et al* 2004 Expression of major histocompatibiltiy complex Class I molecules on the different cell types in multiple sclerosis lesions. *Brain Pathol* **14**: 43–50

Hogan EL, Krigman MNL 1973 Herpes zoster myelitis. *Arch Neurol* **29**: 309–313

Hogg N 2002 The biochemistry and physiology of s-nitrosothiols. *Ann Rev Pharmacol Toxicol* **42**: 585–600

Hogh P, Oturai A, Schreiber K *et al* 2000 Apoliprotein E and multiple sclerosis: impact of the epsilon-4 allele on susceptibility, clinical type and progression rate. *Mult Scler* **6**: 226–230

Hohlfeld R 1997 Biotechnological agents for the immunotherapy of multiple sclerosis: principles, problems and perspectives. *Brain* **120**: 865–916

Hohlfeld R, Wekerle H 2004 Autoimmune concepts of multiple sclerosis as a basis for selective immunotherapy: from pipe dreams to (therapeutic) pipelines. *Proc Natl Acad Sci USA* **101**: 14599–14606

Hohlfeld R, Wekerle H 2005 Using monoclonal antibodies to treat multiple sclerosis. *Nature Clin Pract* (in press)

Hohlfeld R, Wiendl H 2001 The ups and downs of multiple sclerosis therapeutics. *Ann Neurol* **49**: 281–284

Hohlfeld R, Kerschensteiner M, Stadelmann C *et al* 2000 The neuroprotective effect of inflammation: implications for the therapy of multiple sclerosis. *J Neuroimmunol* **107**: 161–166

Hohol MJ, Guttmann CR, Orav J *et al* 1997 Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis. *Arch Neurol* **54**: 1018–1025

Hohol MJ, Olek MJ, Orav EJ *et al* 1999 Treatment of progressive multiple sclerosis

with pulse cyclophosphamide/ methylprednisolone: response to therapy is linked to the duration of progressive disease. *Mult Scler* **5**: 403–409
Hoitsma E, Faber CG, Drent M, Sharma OP 2004 Neurosarcoidosis: a clinical dilemma. *Lancet Neurol* **3**: 397–407
Hoke A, Silver J 1994 Heterogeneity among astrocytes in reactive gliosis. *Pers Dev Neurobiol* **2**: 269–274
Hollinger P, Sturzenegger M, Mathis J *et al* 2002 Acute disseminated encephalomyelitis in adults: a reappraisal of clinical, CSF, EEG and MRI findings. *J Neurol* **249**: 320–329
Holmans P 1993 Asymptotic properties of affected sib-pair linkage analysis. *Am J Hum Genet* **52**: 362–374
Holmes FF, Stubbs DW, Larsen WE 1967 Systemic lupus erythematosus and multiple sclerosis in identical twins. *Arch Int Med* **119**: 302–304
Holmes G 1906 On the relation between loss of function and structural change in focal lesions of the central nervous system, with special reference to secondary degeneration. *Brain* **29**: 514–523
Holmes G 1922 Clinical symptoms of cerebellar disease and their interpretation. Lancet **i**: 1177–82, 1231–37: **ii**: 59–65, 111–115
Holscher C 1997 Nitric oxide, the enigmatic neuronal messenger: its role in synaptic plasticity. *Trends Neurosci* **20**: 298–303
Holt GR, Koch C 1999 Electrical interactions via the extracellular potential near cell bodies. *J Computational Neurosci* **6**: 169–184
Holt S, Hudgins D, Krishnan KR, Critchley EM 1976 Diffuse myelitis associated with rubella vaccination. *Br Med J* **2**: 1037–1038
Hommes OR, Sorensen PS, Fazekas F *et al* for the European Study on Immunoglobulin in multiple sclerosis trialists 2004 Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomised placebo-controlled trial. *Lancet* **364**: 1149–1156
Honan WP, Heron JR, Foster DH *et al* 1990 Visual loss in multiple sclerosis and its relation to previous optic neuritis, disease duration and clinical classification. *Brain* **113**: 975–987
Hong S, Scherer DC, Singh N *et al* 1999 Lipid antigen presentation in the immune system: lessons learned from CD1d knock-out mice. *Immunol Rev* **169**: 44
Hong S, Wilson MT, Serizawa I *et al* 2001 The natural killer T-cell ligand α-galactosyl-ceramide prevents autoimmune diabetes in non-obese diabetic mice. *Nature Med* **7**: 1052–1056
Honig LS 1992 Paroxysmal kinesigenic choreoathetosis. *J Neurol Neurosurg Psychiatry* **55**: 982
Honkaniemi J, Dastidar P, Kahara V, Haapasalo H 2001 Delayed MR imaging changes in acute disseminated encephalomyelitis. *Am J Neuroradiol* **22**:1117–1124
Honmou O, Utzschneider DA, Rizzo MA *et al* 1994 Delayed depolarization and slow sodium currents in cutaneous afferents. *J Neurophysiol* **71**: 1627–1637
Honmou O, Felts PA, Waxman SG, Kocsis JD 1996 Restoration of normal conduction properties in demyelinated spinal cord axons in the adult rat by transplantation of exogenous Schwann cells. *J Neurosci* **16**: 3199–3208
Honnorat J, Saiz A, Giometto B *et al* 2001 Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: study of 14 patients. *Arch Neurol* **58**: 225–230
Hooge JP, Redekop WK 1992 Multiple sclerosis with very late onset. *Neurology* **42**: 1907–1910
Hooge JP, Redekop WK 1995 Trigeminal neuralgia in multiple sclerosis. *Neurology* **45**: 1294–1296
Hoogervorst ELJ, Kalkers NF, van Winsen LML *et al* 2001 Differential treatment effect on measures of neurologic exam, functional impairment and patient self-report in multiple sclerosis. *Mult Scler* **7**: 335–339
Hoogervorst ELJ, Polman CH, Barkhof F 2002 Cerebral volume changes in multiple sclerosis patients treated with high-dose intravenous methylprednisolone. *Mult Scler* **8**: 415–419
Hoogervorst ELJ, Zwemmer JNP, Jelles B *et al* 2004 Multiple Sclerosis Impact Scale (MSIS-29): relation to established measures of impairment and disability. *Mult Scler* **10**: 569–574
Hoogstraten MC, Minderhoud JM 1990 Long term effect of ACTH treatment of relapse in multiple sclerosis. *Acta Neurol Scand* **82**: 74–77
Hoogstraten MC, Cats A, Minderhoud JM 1987 Bed rest and ACTH in the treatment of exacerbations in multiple sclerosis patients. *Acta Neurol Scand* **76**: 346–350
Hoogstraten MC, van der Ploeg RJO, Burg W vd, Vreeling A, van Marle S, Minderhoud JM 1988 Tizanidine versus baclofen in the treatment of spasticity in multiple sclerosis patients. *Acta Neurol Scand* **77**: 224–230
Hooper DC, Bagasra O, Marini JC *et al* 1997 Prevention of experimental allergic encephalomyelitis by targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. *Proc Natl Acad Sci USA* **94**: 2528–2533
Hooper DC, Scott GS, Zborek A *et al* 2000 Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood–CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. *J Fed Am Soc Exp Biol* **14**: 691–698
Hooper J, Whittle IR 1998 Long-term outcome after thalamotomy for movement disorders in multiple sclerosis. *Lancet* **352**: 1984
Hooper R 1826 *The Morbid Anatomy of the Human Brain, illustrated by coloured engravings of the most frequent and important organic diseases to which that viscus is the subject*. London: Longman, Rees, Orme, Brown & Longman
Hooper-van Veen T, Schrijver HM, Zwiers A *et al* 2003 The interleukin-1 gene family in multiple sclerosis susceptibility and disease course. *Mult Scler* **9**: 535–539
Hopf HC, Stamatovic AM, Wahren W 1970 Die cerebralen Anfällen bei der multiplen Sklerose. *J Neurol* **198**: 256–279
Hopkins RS, Indian RW, Pinnow E, Conomy J 1991 Multiple sclerosis in Galion, Ohio: prevalence and results of a case-control study. *Neuroepidemiology* **10**: 192–199
Hopkins SJ, Rothwell NJ 1995 Cytokines and the nervous system. 1: Expression and recognition. *Trends Neurosci* **18**: 83–88
Hopper CL, Matthews CG, Cleeland CS 1972 Symptom instability and thermoregulation in multiple sclerosis. *Neurology* **22**: 142–148
Hornabrook RSL, Miller DH, Newton MR *et al* 1992 Frequent involvement of the optic radiation in patients with acute isolated optic neuritis. *Neurology* **42**: 77–79
Hornabrook RW 1971 The prevalence of multiple sclerosis in New Zealand. *Acta Neurol Scand* **47**: 426–438
Horner PJ, Power AE, Kempermann G *et al* 2000 Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *J Neurosci* **20**: 2218–2228
Horton BT, Wagener HP 1948 Retrobulbar neuritis treatment with histamine. *J Lab Clin Med* **33**: 1611–1612
Horton BT, Wagener HP Aiat JA, Woltman HW 1944 Treatment of multiple sclerosis by the intravenous administration of histamine. *J Am Med Assoc* **124**: 800–801
Horton R, Wilming L, Rand V *et al* 2004 Gene map of the extended human MHC. *Nature Rev Genet* **5**: 889–899
Horvath R, Abicht A, Shoubridge EA *et al* 2000 Leber's hereditary optic neuropathy presenting as multiple sclerosis-like disease of the CNS. *J Neurol* **247**: 65–67
Hosokawa M, Klegeris A, Maguire J, McGeer PL 2003 Expression of complement messenger RNAs and proteins by human oligodendroglial cells. *Glia* **42**: 417–423
Hostetler JA 1974 *The Hutterite Society*. Baltimore, MD: Johns Hopkins University Press
Hostettler ME, Knapp PE, Carlson SL 2002 Platelet-activating factor induces cell death in cultured astrocytes and oligodendrocytes: involvement of caspase-3. *Glia* **38**: 228–239
Hotopf MH, Pollock S, Lishman WA 1994 An unusual presentation of multiple sclerosis. *Psychol Med* **24**: 525–528
Hou JB, Zhang ZX 1992 Prevalence of multiple sclerosis: a door to door survey in Lan Cang La Hu Zu autonomous county, Yunnan Province of China. *Neuroepidemiology* **11**: 52
Houshmand M, Sanati MH, Rashedi I *et al* 2004 Lack of association between Leber's hereditary optic neuropathy primary point mutations and multiple sclerosis in Iran. *Eur Neurol* **51**: 68–71
Houtchens MK, Richert JR, Sami A, Rose JW 1997 Open label gabapentin treatment for pain in multiple sclerosis. *Mult Scler* **3**: 250–253
Houzen H, Niino M, Kikuchi S *et al* 2003 The prevalence and clinical characteristic of MS in northern Japan. *J Neurol Sci* **211**: 49–53

Hoverd PA, Fowler CJ 1998 Desmopressin in the treatment of daytime urinary frequency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **65**: 778–780

Howard AK, Li DKB, Oger J 2003 MRI contributes to the differentiation between MS and HTLV-1 associated myelopathy in British Columbian coastal natives. *Can J Neurol Sci* **30**: 41–48

Howard RS, Wiles CM, Hirsch NP, Loh L, Spencer GT, Newsom-Davis J 1992 Respiratory involvement in multiple sclerosis. *Brain* **115**: 479–494

Howard RS, Greenwood R, Gawler J *et al* 1993 A familial disorder associated with palatal myoclonus, other brainstem signs, tetraparesis, ataxia and Rosenthal fibre formation. *J Neurol Neurosurg Psychiatry* **56**: 977–981

Howe JF, Calvin WH, Loeser JD 1976 Impulses reflected from dorsal root ganglia and from focal nerve injuries. *Brain Res* **116**: 139–144

Howell MD, Winters ST, Olee T *et al* 1989 Vaccination against experimental allergic encephalomyelitis with T cell receptor peptides. *Science* **246**: 668–670

Howell WM, Sage DA, Evans PR *et al* 1991 No association between susceptibility to multiple sclerosis and HLA-DPB1 alleles in the French Canadian population. *Tissue Antigens* **37**: 156–160

Hsieh J, Aimone JB, Kaspar BK *et al* 2004 IGF-I instructs multipotent adult neural progenitor cells to become oligodendrocytes. *J Cell Biol* **164**: 111–122

Hu S, Sheng WS, Ehrlich LC *et al* 2000 Cytokine effects on glutamate uptake by human astrocytes. *Neuroimmunomodulation* **7**: 153–159

Hua LL, Liu JSH, Brosnan CF, Lee SC 1998 Selective inhibition of human glial inducible nitric oxide synthase by interferon-beta: implications for multiple sclerosis. *Ann Neurol* **43**: 384–387

Huang C-C, Chu N-S, Chen T-J, Shaw M-S 1988 Acute haemorrhagic leucoencephalitis with a prolonged clinical course. *J Neurol Neurosurg Psychiatry* **51**: 870–874

Huang D, Han Y, Rani MR *et al* 2000 Chemokines and chemokine receptors in inflammation of the nervous system: manifold roles and exquisite regulation. *Immunol Rev* **177**: 52–67

Huang E, The BS, Zeck O *et al* 2002 Gamma knife radiosurgery for treatment of trigeminal neuralgia in multiple sclerosis patients. *Stereotactic Funct Neurosurg* **79**: 44–50

Huang QR, Teutsch SM, Buhler MMcW *et al* 2000 Evaluation of the Apo-1/Fas promoter Mva 1 polymorphism in multiple sclerosis. *Mult Scler* **6**: 14–18

Huang W-X, He B, Hillert J 1996 An interleukin-1 receptor antagonist gene polymorphism is not associated with multiple sclerosis. *J Neuroimmunol* **67**: 143–144

Huang YM, Hussien Y, Jin YP *et al* 2001a Multiple sclerosis: deficient in vitro responses of blood mononuclear cells to IFN-beta. *Acta Neurol Scand* **104**: 249–256

Huang YM, Hussien Y, Yarilin D *et al* 2001b Interferon-beta induces the development of type 2 dendritic cells. *Cytokine* **13**: 264–271

Huang YM, Kouwenhoven M, Jin YP *et al* 2001c Dendritic cells derived from patients with multiple sclerosis show high CD1a and low CD86 expression. *Mult Scler* **7**: 95–99

Huang YM, Stoyanova N, Jin YP *et al* 2001d Altered phenotype and function of blood dendritic cells in multiple sclerosis are modulated by IFN-beta and IL-10. *Clin Exp Immunol* **124**: 306–314

Hübbe P, Dam AM 1973 Spastic paraplegia of unknown origin: a follow-up of 32 patients. *Acta Neurol Scand* **49**: 536–542

Huber M, Bamborschke S, Assheuer J, Heib WD 1988 Intravenous natural beta interferon treatment of chronic exacerbating-remitting multiple sclerosis: clinical response and MRI/CSF findings. *J Neurol* **235**: 171–173

Huber O 1895 Zur pathol̈schen Anatomie der multiplen Sklerose der Ruckenmarks. *Arch pathologïsche Anat* **140**: 396–410

Huber S, Kappos L, Fuhr P *et al* 1999 Combined acute disseminated encephalomyelitis and acute motor axonal neuropathy after vaccination for hepatitis A and infection with *Campylobacter jejuni*. *J Neurol* **246**: 1204–1206

Hughes GRV 1983 Thrombosis, abortion, cerebral disease and the lupus anticoagulant. *Br Med J* **287**: 1088–1089

Hughes GRV 2003 Migraine, memory loss, and 'multiple sclerosis': neurological features of the antiphospholipid (Hughes) syndrome. *Postgrad Med J* **79**: 81–83

Hughes JC, Enderby PM, Langton HR 1994 Dysphagia and multiple sclerosis: a study and discussion of its nature and impact. *Clin Rehab* 8: 18–26

Hughes JT 1978 *Pathology of the Spinal Cord*, 2nd edn. London: Lloyd-Luke

Hughes PJ, Kirk PF, Dyas J *et al* 1988 Factors influencing circulating OKT8 cell phenotypes in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **50**: 1156–1159

Hughes RAC, Mair WGP 1977 Acute necrotic myelopathy with pulmonary tuberculosis. *Brain* **100**: 223–238

Huh GS, Boulanger LM, Du H *et al* 2000 Functional requirement for class I MHC in CNS development and plasticity. *Science* **290**: 2155–2159

Huitinga I, Van Rooijen N, De Groot CJA *et al* 1990 Suppression of experimental allergic encephalomyelitis in Lewis rats after elimination of macrophages. *J Exp Med* **172**: 1025–1033

Huitinga I, Ruuls SR, Jung S *et al* 1995 Macrophages in T cell line mediated, demyelinating, and chronic-relapsing experimental autoimmune encephalomyelitis in Lewis rats. *Clin Exp Immunol* **100**: 344–351

Huitinga I, Erkut ZA, van Beurden D, Swabb DF 2004 Impaired hypothalamus-pituitary-adrenal axis activity and more severe multiple sclerosis with hypothalamic lesions. *Ann Neurol* **55**: 37–45

Huizar P, Kuno M, Miyata Y 1975 Electrophysiological properties of spinal motoneurones of normal and dystrophic mice. *J Physiol* **248**: 231–246

Huizinga TWJ, Westendorp RGJ, Bollen ELEM *et al* 1997 TNF-α promotor polymorphisms, production and susceptibility to multiple sclerosis in different groups of patients. *J Neuroimmunol* **72**: 149–153

Hull TP, Bates JH 1997 Optic neuritis after influenza vaccination. *Am J Ophthalmol* **124**: 703–704

Hulshof S, Montagne L, DeGroot CJ, Van der Valk P 2002 Cellular localization and expression patterns of interleukin-10, interleukin-4 and their receptors in multiple sclerosis lesions. *Glia* **38**: 24–35

Hulter BM, Lundberg PO 1995 Sexual function in women with advanced multiple sclerosis. *J Neurol Neurosurg Psychiatry* **59**: 83–86

Hume AL,Waxman SG 1988 Evoked potentials in suspected multiple sclerosis: diagnostic value and prediction of clinical course. *J Neurol Sci* **83**: 191–210

Hung T-P 1982 MS in Taiwan – a reappraisal. In: Kuroiwa Y, Kurland L (eds) *Multiple Sclerosis: East and West*. Fukuoka, Japan: Kyuhu University Press, pp. 83–96

Hunter KE, Sporn MB, Davies AM 1993 Transforming growth factor-betas inhibit mitogen-stimulated proliferation of astrocytes. *Glia* **7**: 203–211

Hunter MI, Nlemadim BC, Davidson DL 1985 Lipid peroxidation products and antioxidant proteins in plasma and cerebrospinal fluid from multiple sclerosis patients. *Neurochem Res* **10**: 1645–1652

Hunter SB, Ballinger WE, Rubin JJ 1987 Multiple sclerosis mimicking primary brain tumour. *Arch Pathol Lab Med* **111**: 464–468

Hunter SF, Hafler DA 2000 Ubiquitous pathogens: links between infection and autoimmunity in MS? *Neurology* **55**:164–165

Huntley GW, Benson DL, Colman DR 2002 Structural remodeling of the synapse in response to physiological activity. *Cell* **108**: 1–4

Hupperts R, Broadley S, Mander A *et al* 2001 Patterns of disease in concordant parent-child pairs with multiple sclerosis. *Neurology* **57**: 290–295

Hurst EW 1941 Acute haemorrhagic leuco-encephalitis, a previously undefined entity. *Med J Aust* **2**: 1–6

Huseby ES, Liggitt D, Brabb T *et al* 2001 A pathogenic role for myelin-specific CD8+ T-cells in a model for multiple sclerosis. *J Exp Med* **194**: 669–676

Hussien Y, Sanna A, Soderstrom M *et al* 2001 Glatiramer acetate and IFN-beta act on dendritic cells in multiple sclerosis. *J Neuroimmunol* **121**: 102–110

Hutchins M, Weller RO 1986 Anatomical relationships of the pia mater to cerebral blood vessels in man. *Neurosurgery* **65**: 316–325

Hutchinson M 1993 Pregnancy in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **56**: 1043–1045

Hutchinson M, Bresnihan B 1983 Neurological lupus erythematosus with tonic seizures simulating multiple sclerosis. *J Neurol Neurosurg Psychiatry* **46**: 583–585

Hutchinson WM 1976 Acute optic neuritis and the prognosis for multiple sclerosis. *J Neurol Neurosurg Psychiatry* **39**: 283–289

Hutter CDD, Laing P 1996 Multiple sclerosis: sunlight, diet, immunology and aetiology. *Med Hypotheses* **46**: 67–74

Huynh HK, Oger J, Dorovini-Zis K 1995 Interferon-β down-regulates interferon-γ induced class II molecule expression and morphological changes in primary cultures of human brain microvessel endothelial cells. *J Neuroimmunol* **60**: 63–73

Hwang JM, Chang BL, Park SS 2001 Leber's hereditary optic neuropathy mutations in Korean patients with multiple sclerosis. *Ophthalmologica* **215**: 398–400

Hyllested K 1956 *Disseminated Sclerosis in Denmark: Prevalence and Geographical Distribution*, Copenhagen: J Jorgensen

Hyllested K 1961 Lethality, duration, and mortality of disseminated sclerosis in Denmark. *Acta Psychiatr Scand* **36**: 553–564

Hyllested K 1966 On the prognosis of retrobulbar neuritis. *Acta Ophthalmol* **44**: 246–252

Hyman N, Barnes M, Bhakta B *et al* 2000 Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. *J Neurol Neurosurg Psychiatry* **68**: 707–712

Hynson JL, Kornberg AJ, Coleman LT *et al* 2001 Clinical and neuroradiological features of acute disseminated encephalomyelitis in children. *Neurology* **56**: 1308–1312

Iannucci G, Mascalchi M, Salvi F, Filippi M 2000a Vanishing Balo-like lesions in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **69**: 399–400

Iannucci G, Tortorella C, Rovaris M *et al* 2000b Prognostic value of MR and magnetization transfer imaging findings in patients with clinically isolated syndromes suggestive of multiple sclerosis at presentation. *Am J Neuroradiol* **21**: 1034–1038

Ibrahim MZM, Adams CWM 1963 The relationship between enzyme activity and neuroglia in plaques of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **26**: 101–110

Ibrahim MZM, Adams CWM 1965 The relation between enzyme activity and neuroglia in early plaques of multiple sclerosis. *J Pathol Bacteriol* **90**: 239–243

Ibsen SJ, Clausen J 1995 Genetic susceptibility to multiple sclerosis may be linked to polymorphism of the myelin basic protein gene. *J Neurol Sci* **131**: 96–98

Idrissova ZhR, Boldyreva MN, Dekonenko EP *et al* 2003 Acute disseminated encephalomyelitis in children: clinical features and HLA-DR linkage. *Eur J Neurol* **10**: 537–546

IFNB Multiple Sclerosis Study Group 1993 Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. 1. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* **43**: 655–661

IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group 1995 Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomised controlled trial. *Neurology* **45**: 1277–1285

IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group 1996 Neutralising antibodies during treatment of multiple sclerosis with interferon beta-1b: experience during the first three years. *Neurology* **47**: 889–894

Igarashi M, Schaumburg HH, Powers I *et al* 1976 Fatty acid abnormalities in adrenoleukodystrophy. *J Neurochem* **26**: 851–860

Ijdo JW, Conti-Kelly AM, Greco P *et al* 1999 Anti-phospholipid antibodies in patients with multiple sclerosis and MS-like illnesses: MS or APS? *Lupus* **8**: 109–115

Ikuta F, Zimmerman HM 1976 Distribution of plaques in seventy autopsy cases of multiple sclerosis in the United States. *Neurology* **26**: 26–28

Ikuta K, Ogura T, Shimizu A, Honjo T 1985 Low frequency of somatic mutation in β-chain variable region genes of human T cell receptors. *Proc Natl Acad Sci USA* **82**: 7701–7705

Illés Z, Kondo T, Newcombe J *et al* 2000 Differential expression of NK T cells Va24JaQ invariant TCR chain in the lesions of multiple sclerosis and chronic inflammatory demyelinating polyneuropathy. *J Immunol* **164**: 4375–4381

Ilonen J, Herva E, Reunanen M *et al* 1977 HLA antigens and antibody responses to measles and rubella viruses in multiple sclerosis. *Acta Neurol Scand* **55**: 299–309

Ilyas AA, Chen ZW, Cook SD 2003 Antibodies to sulfatides in the cerebrospinal fluid of patients with multiple sclerosis. *J Neuroimmunol* **139**: 76–80

Imaizumi T, Lankford KL, Waxman SG *et al* 1998 Transplanted olfactory ensheathing cells remyelinate and enhance axonal conduction in the demyelinated dorsal columns of the rat spinal cord. *J Neuroscience* **18**: 6176–6185

Imaizumi T, Lankford KL, Kocsis JD 2000 Transplantation of olfactory ensheathing cells or Schwann cells restores rapid and secure conduction across the transected spinal cord. *Brain Res* **854**: 70–78

Ingalls TH, Huguenin I, Ghent T 1989 Clustering of multiple sclerosis in Galion, Ohio, 1982–1985. *Am J Forensic Med Pathol* **10**: 213–215

Ingle GT, Stevenson VL, Miller DH, Thompson AJ 2003 Primary progressive multiple sclerosis: a 5-year clinical and MR study. *Brain* **126**: 2528–2536

Ingle GT, Sastre-Garriga J, Miller DH, Thompson AJ 2005 Is inflammation important in early PPMS? A longitudinal MRI study. *J Neurol Neurosurg Psychiatry* [epub ahead of print]

Inglese M, Salvi F, Iannucci G *et al* 2002a Magnetization transfer and diffusion tensor MR imaging of acute disseminated encephalomyelitis. *Am J Neuradiol* **23**: 267–272

Inglese M, Ghezzi A, Bianchi S *et al* 2002b Irreversible disability and tissue loss in multiple sclerosis: a conventional and magnetization transfer magnetic resonance imaging study of the optic nerves. *Arch Neurol* **59**: 250–255

Inglese M, van Waesberghe JHTM, Rovaris M *et al* 2003 The effect of interferon β-1b on quantities derived from MT MRI in secondary progressive MS. *Neurology* **60**: 853–860

Inglese M, Mancardi GL, Pagani E *et al* 2004 Brain tissue loss occurs after suppression of enhancement in patients with multiple sclerosis treated with autologous haematopoietic stem cell transplantation. *J Neurol Neurosurg Psychiatry* **75**: 643–644

Ingram DA, Swash M, Thompson AJ 1987 Clinical evaluation of magnetic brain stimulation in degenerative and demyelinating disorders of the CNS. *Electroencephalogr Clin Neurophysiol* **66**: S122

Innes JRM, Kurland LT 1952 Is multiple sclerosis caused by a virus? *Am J Med* **12**: 574–585

International Human Genome Sequencing Consortium 2001 Initial sequencing and analysis of the human genome. *Nature* **40**: 860–921

International Multiple Sclerosis Genetics Consortium 2005 A high density screen for linkage in multiple sclerosis. *Am J Hum Genet* **77**: 454–467

International Study Group for Behcet's Disease 1990 Criteria for diagnosis of Behcet's disease. *Lancet* **335**: 1078–1080

Ipsen J 1950 Life expectancy and probable disability in multiple sclerosis. *N Engl J Med* **243**: 909–913

Irani DN, Kerr DA 2000 14–3–3 protein in the cerebrospinal fluid of patients with acute transverse myelitis. *Lancet* **355**: 901

Iriarte J, De Castro P 2002 Fatigue is not associated with raised inflammatory markers in multiple sclerosis. *Neurology* **58**: 1134–1135

Iriarte J, Subira ML, Castro P 2000 Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. *Mult Scler* **6**: 124–130

Isaac C, Li DK, Genton M *et al* 1988 Multiple sclerosis: a serial study using MRI in relapsing patients. *Neurology* **38**: 1511–1515

Isaacs JD, Watts RA, Hazleman BL *et al* 1992 Humanised monoclonal antibody therapy for rheumatoid arthritis. *Lancet* **340**: 748–752

Isager H, Anderson k, Hyllested K 1980 Risk of multiple sclerosis inversely associated with birth-order position. *Acta Neurol Scand* **61**: 393–396

Isayama Y, Takahashi T, Shimoyoma T, Yamadori A 1982 Acute optic neuritis and multiple sclerosis. *Neurology* **32**: 73–76

Isbister CM, Mackenzie PJ, Anderson D *et al* 2003 Co-occurrence of multiple sclerosis and myasthenia gravis in British Columbia. *Mult Scler* **9**: 550–553

Ishibashi M, McMahon AP 2002 A sonic hedgehog-dependent signaling relay regulates growth of diencephalic and mesencephalic primordia in the early mouse embryo. *Development* **129**: 4807–4819

Ishigami T, White CA, Pender MP 1998 Soluble antigen therapy induces apoptosis of autoreactive T cells preferentially in the target organ rather than in the peripheral lymphoid organs. *Eur J Immunol* **28**: 1626–1635

Ishikawa K, Tanaka M, Black JA, Waxman SG 1999 Changes in expression of voltage-gated potassium channels in dorsal root ganglion neurons following axotomy. *Muscle Nerve* **22**: 502–507

Isler W 1961 Multiple Sklerose im Kindersalter. *Helvetica Pediatrica Acta* **16**: 412–431

Issazadeh S, Ljungdahl Å, Höjeberg B *et al* 1995a Cytokine production in the central nervous system of Lewis rats with experimental autoimmune encephalomyelitis: dynamics of mRNA expression for interleukin-10, interleukin-12, cytolysin, tumor necrosis factor α and tumor necrosis factor β. *J Neuroimmunol* **61**: 205–212

Issazadeh S, Mustafa M, Ljungdahl Å *et al* 1995b Interferon γ, interleukin 4 and transforming growth factor β in experimental autoimmune encephalomyelitis in Lewis rats: dynamics of cellular mRNA expression in the central nervous system and lymphoid cells. *J Neurosci Res* **40**: 579–590

Issazadeh S, Navikas V, Schaub M *et al* 1998 Kinetics of expression of costimulatory molecules and their ligands in murine relapsing experimental autoimmune encephalomyelitis in vivo. *J Immunol* **161**: 1104–1112

Ito M, Blumberg BM, Mock DJ *et al* 2001 Potential environmental and host participants in the early white matter lesion of adreno-leukodystrophy: morphologic evidence for CD8 cytotoxic T cells, cytolysis of oligodendrocytes and CD1 mediated lipid antigen presentation. *J Neuropath Exp Neurol* **60**: 1004–1019

Itoh T, Aizawa H, Hashimoto K *et al* 2003 Prevalence of multiple sclerosis in Asahikawa, a city in northern Japan. *J Neurol Sci* **214**: 7–9

Itoyama Y, Sternberger NH, Webster HdeF *et al* 1980 Immunocytochemical observation on the distribution of myelin-associated glycoprotein and myelin basic protein in multiple sclerosis lesions. *Ann Neurol* **7**: 167–177

Itoyama Y, Webster HD, Sternberger NH *et al* 1982 Distribution of papovavirus, myelin associated glycoprotein, and myelin basic protein in progressive multifocal leukoencephalopathy lesions. *Ann Neurol* **11**: 396–404

Itoyama Y, Webster Hde F, Richardson EP Jr, Trapp BD 1983 Schwann cell remyelination of demyelinated axons in spinal cord multiple sclerosis lesions. *Ann Neurol* **14**: 339–346

Itoyama Y, Ohnishi A, Tateishi J *et al* 1985 Spinal cord multiple sclerosis lesions in Japanese patients: Schwann cell remyelination occurs in areas that lack glial fibrillary acidic protein. *Acta Neuropathol* **65**: 217–223

Ivanova A, Nakahira E, Kagawa T *et al* 2003 Evidence for a second wave of oligodendrogenesis in the postnatal cerebral cortex of the mouse. *J Neurosci Res* **73**: 581–92

Iversen L 2003 Cannabis and the brain. *Brain* **126**: 1252–1270

Ivnik RJ 1978 Neuropsychological test performance as a function of the duration of MS-related symptomatology. *J Clin Psychiatry* **39**: 304–307

Izikson L, Klein RS, Charo IF *et al* 2000 Resistance to experimental autoimmune encephalomyelitis in mice lacking the CC chemokine receptor (CCR)2. *J Exp Med* **192**: 1075–1080

Izquierdo G, Lyon-Caen O, Marteau R *et al* 1986 Early onset multiple sclerosis: clinical study of 12 pathologically proven cases. *Acta Neurol Scand* **73**: 493–497

Jabaily J, Thompson J 1997 Effects of interferon beta-1B in rheumatoid arthritis: a case report. *Arthritis Rheum* **40**: 1370

Jabs DA, Mill NR, Newman SA, Johnson MA, Stevens MB 1986 Optic neuropathy in systemic lupus erythematosus. *Arch Ophthalmol* **104**: 564–568

Jackson G, Miller M, Littlejohn G, Helme R, King R 1986 Bilateral internuclear ophthalmoplegia in systemic lupus erythematosus. *J Rheumatol* **13**: 1151–1162

Jacobs LD, O'Malley J, Freeman A, Ekes R 1981 Intrathecal interferon reduces exacerbations of multiple sclerosis. *Science* **214**: 1026–1028

Jacobs LD, O'Malley J, Freeman A, Ekes R 1982 Intrathecal interferon in multiple sclerosis. *Arch Neurol* **39**: 609–615

Jacobs LD, Kinkel PR, Kinkel WR 1986a Silent brain lesions in patients with isolated optic neuritis: a clinical and nuclear magnetic resonance imaging study. *Arch Neurol* **43**: 452–455

Jacobs LD, Salazar AM, Herndon R *et al* 1986b Multicenter double-blind study of effect of intrathecally administered natural human fibroblast interferon on exacerbations of multiple sclerosis. *Lancet* **ii**: 1411–1414

Jacobs LD, Salazar AM, Herndon R *et al* 1987 Intrathecally administered natural human fibroblast interferon reduces exacerbations of multiple sclerosis: results of a multicenter double-blind study. *Arch Neurol* **44**: 589–595

Jacobs LD, Munschauer FE, Kaba SE 1991 Clinical and magnetic resonance imaging in optic neuritis. *Neurology* **41**: 15–19

Jacobs LD, Kaba S, Pullicino P 1994 The lesion causing continuous facial myokymia in multiple sclerosis. *Arch Neurol* **51**: 1115–1119

Jacobs LD, Cookfair DL, Rudick RA *et al* 1995 A phase III trial of intramuscular recombinant interferon beta for exacerbating–remitting multiple sclerosis: design and conduct of study; baseline characteristics of patients. *Mult Scler* **1**: 118–135

Jacobs LD, Cookfair DL, Rudick RA *et al* 1996 Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Ann Neurol* **39**: 285–294

Jacobs LD, Kaba SE, Miller CM *et al* 1997 Correlation of clinical, magnetic resonance imaging, and CSF findings in optic neuritis. *Ann Neurol* **41**: 392–398

Jacobs LD, Beck RW, Simon JH *et al* and the CHAMPS Study Group 2000 Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* **343**: 898–904

Jacobsen M, Schweer D, Ziegler *et al* 2000 A point mutation in *PTPRC* is associated with the development of multiple sclerosis. *Nature Genet* **26**: 495–499

Jacobsen M, Cepok S, Quak E *et al* 2002 Oligoclonal expansion of memory CD8+ T cells in cerebrospinal fluid from multiple sclerosis patients. *Brain* **125**: 538–550

Jacobson DM, Thompson HS, Corbett JJ 1988 Optic neuritis in the elderly: prognosis for visual recovery and long-term follow up. *Neurology* **38**: 1834–1837

Jacobson DM, Marx JJ, Dlesk A 1991 Frequency and clinical significance of Lyme seropositivity in patients with isolated optic neuritis. *Neurology* **41**: 706–711

Jacobson DM, Moster ML Eggenberger ER *et al* 1999 Isolated trochlear nerve palsy in patients with multiple sclerosis. *Neurology* **53**: 877–879

Jacobson S, Flerlage ML, McFarland HF 1985 Impaired measles virus-specific cytotoxic T cell responses in multiple sclerosis. *J Exp Med* **162**: 839–850

Jacôme DE 1985 La toux diabolique: neurogenic tussive crises. *Postgrad Med J* **61**: 515–516

Jacôme DE 2001 Blepharoclonus in multiple sclerosis. *Acta Neurol Scand* **104**: 380–384

Jahng AW, Maricic I, Pedersen B *et al* 2001 Activation of natural killer T cells potentiates or prevents experimental autoimmune encephalomyelitis. *J Exp Med* **194**: 1789–1799

Jahnke U, Fischer EH, Alvord EC 1985 Sequence homology between certain viral proteins and proteins related to encephalomyelitis and neuritis. *Science* **229**: 282–284

Jain KK 2000 Evaluation of mitoxantrone for the treatment of multiple sclerosis. *Expert Opin Invest Drugs* **9**: 1139–1149

Jain S, Maheshwari M 1985 Multiple sclerosis: Indian experience in the last thirty years. *Neuroepidemiology* **4**: 96–107

Jain S, Proudlock F, Constantinescu CS, Gottlob I 2002 Combined pharmacologic and surgical approach to acquired nystagmus due to multiple sclerosis. *Am J Ophthalmol* **134**: 780–782

Jaing TH, Lin KL, Chiu CH *et al* 2001 Acute disseminated encephalomyelitis in autoimmune hemolytic anemia. *Pediatr Neurol* **24**: 303–305

James PB 1982 Evidence for subacute fat embolism as the cause of multiple sclerosis. *Lancet* **i**: 380–386

Jameson SC, Hogquist KA, Bevan MJ 1995 Positive selection in the thymus. *Ann Rev Immunol* **13**: 93–126

Jamieson J 1886 Cases of multiple neuritis. *Aust Med J* **8**: 295–302

Jander S, Stoll G 1998 Differential induction of interleukin-12, interleukin-18, and interleukin-1-beta converting enzyme mRNA in experimental autoimmune encephalomyelitis of the Lewis rat. *J Neuroimmunol* 91: 93–99

Jander S, Heidenreich F, Stoll G 1993 Serum and CSF levels of solule intercellular adhesion molecule-1 (ICAM-1) in inflammatory neurologic diseases. *Neurology* **43**: 1809–1813

Janeway CA 1992 The T cell receptor as a multicomponent signalling machine: CD4/CD8 coreceptors and CD45 in T cell activation. *Ann Rev Immunol* **10**: 645–674

Jankovic BD, Waksman BH, Arnason BG 1962 Role of the thymus in response to bovine serum immune reactions in rats. The immunologic response to bovine serum albumin (antibody formation, Arthus reactivity, and delayed hypersensitivity) in rats thymectomised or splenectomised at various times after birth. *J Exp Med* **116**: 159–176

Jans H, Heltberg A, Zeeberg I, Kristensen JH, Fog T, Raun NE 1984 Immune complexes and the complement factors C4 and C3 in cerebrospinal fluid and serum from patients with chronic progressive multiple sclerosis. *Acta Neurol Scand* **69**: 34–38

Janssen RS, Kaplan JE, Khabbaz RF *et al* 1991 HTLV-1-associated myelopathy/tropical spastic paraparesis in the United States. *Neurology* **41**: 1355–1357

Jansson M, Panoutsakopoulos V, Baker J *et al* 2002 Cutting edge: attenuated experimental autoimmune encephalomyelitis in eta-1/osteopontin-deficient mice. *J Immunol* **168**: 2096–2099

Janzer RC, Raff MC 1987 Astrocytes induce blood brain barrier properties in endothelial cells. *Nature* **325**: 253–257

Jarrett L, Nandi P, Thompson AJ 2002 Managing severe lower limb spasticity in multiple sclerosis: does intrathecal phenol have a role? *J Neurol Neurosurg Psych* **73**: 705–709

Jean I, Allamargot C, Barthelaix-Pouplard A, Fressinaud C 2002 Axonal lesions and PDGF-enhanced remyelination in the rat corpus callosum after lysolecithin demyelination. *NeuroReport* **13**: 627–631

Jean I, Lavialle C, Barthelaix-Pouplard A, Fressinaud C 2003 Neurotrophin-3 specifically increases mature oligodendrocyte population and enhances remyelination after chemical demyelination of adult rat CNS. *Brain Res* **972**: 110–118

Jedlicka P, Benes B, Hron B *et al* 1994 Epidemiology of MS in the Czech Republic. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 261–265

Jeffery ND, Blakemore WF 1997 Locomotor deficits induced by experimental spinal cord demyelination are abolished by spontaneous remyelination. *Brain* **120**: 27–37

Jeffrey DR, Mandler RN, Davis LE 1993 Transverse myelitis: retrospective analysis of 33 cases with differentiation of cases associated with multiple sclerosis and parainfectious events. *Arch Neurol* **50**: 532–535

Jeffrey DR, Absher J, Pfeiffer FE, Jackson H 2000 Cortical deficits in multiple sclerosis on the basis of subcortical lesions. *Mult Scler* **6**: 50–55

Jeffreys AJ, Kauppi L, Neumann R 2001 Intensely punctate meiotic recombination in the class II region of the major histocompatibility complex. *Nature Genet* **29**: 217–22

Jellinek EH 1990 Heine's illness: the case for multiple sclerosis. *J R Soc Med* **83**: 516–519

Jellinger K 1969 Einige morphologïsche Aspekte der Multiplen Sklerose. *Wiener Z Nervenheilk* **Suppl II**: 12–37

Jenkins HG, Ikeda H 1992 Tumour necrosis factor causes an increase in axonal transport of protein and demyelination in the mouse optic nerve. *J Neurol Sci* **108**: 99–104

Jenkins MK, Khoruts A, Ingulli E *et al* 2001 In vivo activation of antigen specific CD4 T cells. *Annu Rev Immunol* **19**: 23–45

Jennekens-Schinkel A, van der Velde EA, Sanders EACM, Lanser JBK 1989 Visuospatial problem solving, conceptual reasoning and sorting behaviour in multiple sclerosis out-patients. *J Neurol Sci* **90**: 187–202

Jennekens-Schinkel A, Laboyrie PM, Lanser JBK, van der Velde EA 1990 Cognition in patients with multiple sclerosis after 4 years. *J Neurol Sci* **99**: 229–247

Jennett B 1996 Epidemiology of head injury. *J Neurol Neurosurg Psych* **60**: 362–369

Jennings AR, Kirilak Y, Carroll WM 2002 In situ characterisation of oligodendrocyte progenitor cells in adult mammalian optic nerve. *J Neurocytol* **31**: 27–39

Jensen PS, Rasmussen P, Reske-Nielsen E 1982 Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. *Acta Neurol Scand* **65**: 182–185

Jepson RG, Mihaljevic L, Craig J 2004 Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev 1*: CD001321 and CD001321

Jersild C, Svejgaard A, Fog T 1972 HL-A antigens and multiple sclerosis. *Lancet* **i**: 1240–1241

Jersild C, Fog T, Hansen GS *et al* 1973 Histocompatibility determinants in multiple sclerosis, with special reference to clinical course. *Lancet* **ii**: 1221–1225

Jersild C, Kurtzke JF, Riisom K *et al* 1993 Multiple sclerosis in the Faroe Islands. VI Studies of HLA markers. *Tissue Antigens* **42**: 105–110

Jiang F, Frederick TJ, Wood TL 2001 IGF-I synergizes with FGF-2 to stimulate oligodendrocyte progenitor entry into the cell cycle. *Dev Biol* **232**: 414–423

Jiang GX, Cheng Q, Fredrikson S, Link H 1999 First hospital-admission rate as an epidemiological indicatotor for patients with multiple sclerosis in Stockholm 1984–1993. *Acta Neurol Scand* **100**: 64–68

Jiang H, Zhang S-L, Pernis B 1992 Role of $CD8^+$ T cells in murine experimental allergic encephalomyelitis. *Science* **256**: 1213–1215

Jiang H, Milo R, Swoveland P *et al* 1995 Interferon β-1b reduces interferon γ-induced antigen-presenting capacity of human glial and B cells. *J Neuroimmunol* **61**: 17–25

Jiang H, Braunstein NS, Yu B *et al* 2001 $CD8^+$ T cells control the TH phenotype of MBP-reactive $CD4^+$ T cells in EAE mice. *Proc Natl Acad Sci USA* **98**: 6301–6306

Jiang Y, Jahagirdar BN, Reinhardt RL *et al* 2002 Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* **418**: 41–49

Jiang Y, Henderson D, Blackstad M *et al* 2003 Neuroectodermal differentiation from mouse multipotent adult progenitor cells. *Proc Natl Acad Sci USA* **100**: 11854–11860

Jimenez-Jimenez FJ, Zurdo JM, Hernanz A *et al* 2002 Tau protein concentrations in cerebrospinal fluid of patients with multiple sclerosis. *Acta Neurol Scand* **106**: 351–354

Jimi T, Wakayama 1993 Mexilitene for the treatment of spasticity due to neurological disorders. *Muscle Nerve* **16**: 885

Jin J-P, de Pedro-Cuesta J, Soderstrom M *et al* 1998 Incidence of optic neuritis in Stockholm, Sweden 1990–1995: I. Age, sex birth and ethnic-group related patterns. *J Neurol Sci* **159**: 107–114

Jin YP, de Pedro-Cuesta J, Soderstrom M, Link H 1999 Incidence of optic neuritis in Stockholm, Sweden, 1990–1995: II. Time and space patterns. *Arch Neurol* **56**: 975–980

Jin YP, de Pedro-Cuesta J, Soderstrom M *et al* 2000 Seasonal patterns in optic neuritis and multiple sclerosis: a meta-analysis. *J Neurol Sci* **181**: 56–64

Jin YP, de Pedro-Cuesta J, Huang YH, Soderstrom M 2003 Predicting multiple sclerosis at optic neuritis onset. *Mult Scler* **9**: 135–141

Jing W, Patel M, Nathanson M *et al* 1998 Acute transverse myelitis associated with tuberculin skin test (PPD). *Neurology* **50**: 1921–1922

Jirholt J, Lindqvist A, Karlsson J *et al* 2002 Identification of susceptibility genes for experimental autoimmune encephalomyelitis that overcome the effect of protective alleles at the eae2 locus. *Int Immunol* **14**: 79–85

Joannides A, Gaughwin P, Scott M *et al* 2003 Postnatal astrocytes promote neural induction from adult human bone marrow-derived stem cells. *J Hematother Stem Cell Res* **12**: 681–688

Joannides A, Gaughwin P, Schwiening C *et al* 2004 Efficient generation of neural precursors from adult human skin: astrocytes promote neurogenesis from skin-derived stem cells. *Lancet* **364**: 172–178

Joensen P 1992 Parts of Faroese neuroepidemiology. *Ann Soci Sci Faeroensis* **Suppl XVII**: 32

Joffe RT, Lippert GP, Gray TA *et al* 1987 Mood disorder and multiple sclerosis. *Arch Neurol* **44**: 376–378

Johansson CB, Momma S, Clarke DL *et al* 1999 Identification of a neural stem cell in the adult mammalian central nervous system. *Cell* **96**: 25–34

John GR, Shankar SL, Shafit-Zagardo B *et al* 2002 Multiple sclerosis: re-expression of a developmental pathway that restricts oligodendrocyte maturation. *Nature Med* **8**: 1115–1121

Johns CD, Flanders KC, Ranges GE, Sriram S 1991 Successful treatment of experimental allergic encephalomyelitis with transforming growth factor beta 1. *J Immunol* **147**: 1792–1796

Johns LD, Sriram S 1993 Experimental allergic encephalomyelitis: neutralizing antibody to TGF beta 1 enhances the clinical severity of the disease. *J Neuroimmunol* **47**: 1–7

Johns TG, Kerlero de Rosbo N, Menon KK *et al* 1995 Myelin oligodendrocyte glycoprotein induces a demyelinating encephalomyelitis resembling multiple sclerosis. *J Immunol* **154**: 5536–5541

Johns TG, Bernard CC 1997 Binding of complement component Clq to myelin oligodendrocyte glycoprotein: a novel mechanism for regulating CNS inflammation. *Mol Immunol* **34**: 33–38

Johnson GC, Esposito L, Barratt BJ *et al* 2001 Haplotype tagging for the identification of common disease genes. *Nature Genet* **29**: 233–237

Johnson J 2003 On receiving the diagnosis of multiple sclerosis: managing the transition. *Mult Scler* **9**: 82–88

Johnson KP, Knobler RL, Greenstein JL *et al* 1990 Recombinant human beta interferon treatment of relapsing–remitting multiple sclerosis: pilot study results. *Neurology* **40 (Suppl 1)**: 261 (abstract)

Johnson KP, Brooks BR, Cohen JA *et al* 1995 Copolymer 1 reduces relapse rate and improves disability in relapsing–remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-cxontrolled trial. *Neurology* **45**: 1268–1276

Johnson KP, Brooks BR, Cohen JA *et al* 1998 Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group. *Neurology* **50**: 701–708

Johnson KP, Brooks BR, Ford CC *et al* 2000 Sustained clinical benefits of glatiramer acetate in relapsing multiple sclerosis patients observed for 6 years. *Mult Scler* **6**: 255–266

Johnson KP, Brooks BR, Cohen JA *et al* 2001 Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. 1998. *Neurology* **57**: S46–S53

Johnson KP, Brooks BR, Ford CC *et al* 2003 Glatiramer acetate (Copaxone): comparison of continuous versus delayed therapy in a six-year organized multiple sclerosis trial. *Mult Scler* **9**: 585–591

Johnson MR, Ferner RE, Bobrow M *et al* 2000 Detailed analysis of the oligodendrocyte myelin glycoprotein gene in four patients with neurofibromatosis 1 and primary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* **68**: 643–646

Johnson RT 1982 *Viral Infections of the Nervous System*. New York: Raven Press

Johnson RT 1994 The virology of demyelinating diseases. *Ann Neurol* **36 (Suppl)**: 54–60

Johnston JB, Silva C, Holden J *et al* 2001 Monocyte activation and differentiation augment human endogenous retrovirus expression: implications for inflammatory brain diseases. *Ann Neurol* **50**: 434–442

Jolivet Reynaud C, Perron H, Ferrante P *et al* 1999 Specificities of multiple sclerosis cerebrospinal fluid and serum antibodies against mimotopes. *Clin Immunol* **93**: 283–293

Jonasdottir A, Thorlacius T, Fossdal R *et al* 2003 A whole genome association study in Icelandic multiple sclerosis patients with 4804 markers. *J Neuroimmunol* **143**: 88–92

Jones CK, Riddehough A, Li DKB *et al* 2001 MRI cerebral atrophy in relapsing remitting MS: results of the PRISMS trial. *Neurology* **56(Suppl 3)**: A379

Jones J, Frith S, Piddlesden S *et al* 1991 Imaging calcium changes in individual oligodendrocytes attacked by T cell derived perforin. *Immunology* **74**: 572–577

Jones RE, Heron JR, Foster DH *et al* 1983 Effects of 4-aminopyridine in patients with multiple sclerosis. *J Neurol Sci* **60**: 353–362

Jones RF, Burke D, Marosszeky JE, Gillies JD 1970 A new agent for the control of spasticity. *J Neurol Neurosurg Psychiatry* **33**: 464–468

Jones SJ 1993 Somatosensory evoked potentials. II: Clinical observations and applications. In: Halliday AM (ed.) *Evoked Potentials in Clinical Testing*. Edinburgh: Churchill Livingstone, pp. 421–466

Jones SJ, Sprague L, Vaz Pato M 2002 Electrophysiological evidence for a defect in the processing of temporal sound patterns in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **73**: 561–567

de Jong BA, Huizinga TW, Zanelli E *et al* 2002a Evidence for additional genetic risk indicators of relapse-onset MS within the HLA region. *Neurology* **59**: 549–555

de Jong BA, Huizinga TWJ, Bollen ELEM *et al* 2002b Production of IL-1β and IL-1Ra as risk factors for susceptibility and progression of relapse-onset multiple sclerosis. *J Neuroimmunol* **126**: 172–179

de Jong BA, Engelen M, van Schaik IN, Vermeulen M 2005 Confusing Cochrane reviews on treatment in multiple sclerosis. *Lancet Neurol* **4**: 330–331

Jonsson A, Korfitzen EM, Heltberg A *et al* 1993 Effects of neuropsychological treatment in patients with multiple sclerosis. *Acta Neurol Scand* **88**: 394–400

Jonsson L, Thomas K-A, Stenquist M *et al* 1991 Acute peripheral facial palsy simulating Bell's palsy in a case of probable multiple sclerosis with a clinically correlated transient pontine lesion on magnetic resonance imaging. *J Otorhinolaryngol Rel Specialt* **53**: 362–365

Jordan CA, Friedrich VL Jr, Godfraind C *et al* 1989 Expression of viral and myelin gene transcripts in a murine CNS demyelinating disease caused by a coronavirus. *Glia* **2**: 318–329

Josien E, Lefebvre V, Vermesch P, Pasquier F, Petit H 1993 Adrénoleucomyéloneuropathy de l'adulte. *Rev Neurol* **149**: 230–232

Joutel A, Corpechot C, Ducros A *et al* 1996 Notch3 mutations in cadasil, a hereditary adult-onset condition causing stroke and dementia. *Nature* **383**: 707–710

Joyce KA, Rees JE 1995 Transverse myelitis after measles, mumps, and rubella vaccination. *Br Med J* **311**: 422

Juhler M, Barry DI, Offner H *et al* 1984 Blood-brain barrier and blood-spinal cord barrier permeability during the course of experimental allergic encephalomyelitis. *Brain Res* **302**: 347–355

Jung M, Pesheva P, Schachner M, Trotter J 1993 Astrocytes and neurons regulate the expression of the neural recognition molecule janusin by cultured oligodendrocytes. *Glia* **9**: 163–175

Jung S, Siglienti I, Grauer O *et al* 2004 Induction of IL-10 in rat peritoneal macrophages and dendritic cells by glatiramer acetate. *J Neuroimmunol* **148**: 63–73

Jungi TW, Brcic M, Kuhnert P *et al* 1990 Effect of IgG for intravenous use on Fc receptor mediated phagocytosis by human monocytes. *Clin Exp Immunol* **82**: 163–169

Jurewicz A, Matysiak M, Tybor K, Selmaj K 2003 TNF-induced death of adult human oligodendrocytes is mediated by c-jun

NH_2-terminal kinase-3. *Brain* **126**: 1358–1370
Kääb G, Haarmann I, Wekerle H, Bradl M 1998 The myelin basic protein specific T cell repertoire in Lewis rats: T cell receptor diversity is influenced both by intrathymic milieu and by extrathymic peptide presentation. *Eur J Immunol* **28**: 1499–1506
Kabat EA, Moore DH, Landow H 1942 An electrophoretic study of the protein components in cerebrospinal fluid and their relationship to the serum proteins. *J Clin Invest* **21**: 571–577
Kaeser HE 1962 Funktionsprüfungen peripherer Nerven bei experimentellen Polyneuritiden und bei der Wallerschen Degeneration. *Dtsch Z Nervenheilk* **183**: 268–304
Kaeser HE, Lambert EH 1962 Nerve function studies in experimental polyneuritis. *Electroencephalogr Clin Neurophysiol* **22 (Suppl)**: 29–35
Kahana E, Leibowitz U, Alter M 1971 Cerebral multiple sclerosis. *Neurology* **21**: 1179–1185
Kahana E, Leibowitz U, Fishback M, Alter M 1973 Slowly progressive and acute visual impairment in multiple sclerosis. *Neurology* **23**: 729–723
Kahana E, Zilber N, Abramson JH *et al* 1994 Multiple sclerosis: genetic versus environmental aetiology: epidemiology in Israel updated. *J Neurol* **241**: 341–346
Kahn MA, Kusher I 1979 Ankylosing spondylitis and multiple sclerosis: a possible association. *Arthritis Rheum* **22**: 784–786
Kaiboriboon K, Olsen TJ, Hayat GR 2005 Cauda equine and conus medullaris syndrome in sarcoidosis. *Neurologist* **11**: 179–198
Kaiserling E, SteinH, Müller-Hermelink HK 1974 Interdigitating reticulum cells in the human thymus. *Cell Tiss Res* **155**: 47–55
Kaji R, Suzumura A, Sumner AJ 1988 Physiological consequences of antiserum-mediated experimental demyelination in CNS. *Brain* **111**: 675–694
Kaji R, Sumner AJ 1989a Effect of digitalis on central demyelinative conduction block in vivo. *Ann Neurol* **25**: 159–165
Kaji R, Sumner AJ 1989b Ouabain reverses conduction disturbances in single demyelinated nerve fibers. *Neurology* **39**: 1364–1368
Kaji R, Happel L, Sumner AJ 1990 Effect of digitalis on clinical symptoms and conduction variables in patients with multiple sclerosis. *Ann Neurol* **28**: 582–584
Kaji R, Bostock H, Kohara N *et al* 2000 Activity-dependent conduction block in multifocal motor neuropathy. *Brain* **123**: 1602–1611
Kakigi R, Kuroda Y, Neshige R *et al* 1992 Physiological study of the spinothalamic tract conduction in multiple sclerosis. *J Neurol Sci* **107**: 205–209
Kalanie H, Tabatabai SS 1998 Combined immunoglobulin and azathioprine in multiple sclerosis. *Eur Neurol* **39**: 178–181
Kalanie H, Kamgooyan M, Sadeghian H, Kalanie AR 2000 Histocompatibility antigen (HLA) associations with multiple sclerosis in Iran. *Mult Scler* **6**: 317–319
Kalita J, Misra UK, Mandal SK 1998 Prognostic predictors of acute transverse myelitis. *Acta Neurol Scand* **98**: 60–63
Kalkers NF, Bergers E, Castelijns JA *et al* 2001 Optimizing the association between disability and biological markers in MS. *Neurology* **57**: 1253–1258
Kalkers NF, Barkhof F, Bergers E *et al* 2002a The effect of the neuroprotective agent riluzole on MRI parameters in primary progressive multiple sclerosis. *Mult Scler* **8**: 532–533
Kalkers NF, Vrenken H, Uitdehaag BM *et al* 2002b Brain atrophy in multiple sclerosis: impact of lesions and of damage of whole brain tissue. *Mult Scler* **8**: 410–414
Källen B, Nilsson O 1986 Dissociation between histological and clinical signs of experimental autoimmune encephalomyelitis. *Acta Pathol Microbiol Immunol Scand* **94**: 159–164
Kallmann B-A, Sauer J, Schliesser M *et al* 2004 Determination of ventricular diameters in multiple sclerosis patients with transcranial sonography: a two year follow up study. *J Neurol* **251**: 30–34
Kalman B, Leist TP 2003 A mitochondrial component of neurodegeneration in multiple sclerosis. *Neuromol Med* **3**: 147–158
Kalman B, Mandler RN 2002 Studies of mitochondrial DNA in Devic's disease revealed no pathogenic mutations, but polymorphisms also found in association with multiple sclerosis. *Ann Neurol* **51**: 661–662
Kalman B, Takacs K, Gyodin E *et al* 1991 Sclerosis multiplex in gypsies. *Acta Neurol Scand* **84**: 181–185
Kalman B, Lublin FD, Alder H 1996 Characterisation of the mitochondrial DNA in patients with multiple sclerosis. *J Neurol Sci* **140**: 75–89
Kalman B, Rodriguez-Valdez JL, Bosch U, Lublin FD 1997 Screening for Leber's hereditary optic neuropathy associated mitochondrial DNA mutations in patients with prominent optic neuritis. *Mult Scler* **2**: 279–282
Kalman B, Li S, Chatterjee D *et al* 1999 Large scale screening of the mitochondrial DNA reveals no pathogenic mutations but a haplotype associated with multiple sclerosis in Caucasians. *Acta Neurol Scand* **99**: 16–25
Kamalian N, Keesey RE, ZuRhein GM 1975 Lateral hypothalamic demyelination and cachexia in a case of 'malignant' multiple sclerosis. *Neurology* **25**: 25–30
Kamme F, Salunga R, Yu JX *et al* 2003 Single-cell microarray analysis in hippocampus CA1: demonstration and validation of cellular heterogeneity. *J Neurosci* **23**: 3607–3615
Kanchandani R, Howe JG 1982 Lhermitte's sign in multiple sclerosis: a clinical survey and review of the literature. *J Neurol Neurosurg Psychiatry* **45**: 308–312
Kanda T, Iwasaki T, Yamawaki M *et al* 2000 Anti-GM1 antibody facilitates leakage in an in vitro blood–nerve barrier model. *Neurology* **55**: 585–587
Kandel ER, Schwartz JH 1985 *Principles of Neural Science*. New York: Elsevier
Kane M 1995 Global programme for control of hepatitis B infection. *Vaccine* **13 (Suppl 1)**: S47–S49
Kankonkar S, Jeyanti G, Singhal BS, Shankarkumar U 2003 Evidence for novel DRB1*15 allele association among clinically definite multiple sclerosis patients from Mumbai, India. *Hum Immunol* **64**: 478–482
Kanpolat Y, Berk C, Savas A, Bekar A 2000 Percutaneous controlled radiofrequency rhizotomy in the management of patients with trigeminal neuralgia due to multiple sclerosis. *Acta Neurochir* **142**: 685–689; discussion 689–690
Kansu T, Kirkali P, Kansu E, Zileli T 1989 Optic neuropathy in Behçet's disease. *J Clin Neuroophthalmol* **9**: 277–280
Kantarci O, Siva A, Eraksoy M *et al* 1998 Survival and predictors of disability in Turkish MS patients. Turkish Multiple Sclerosis Study Group (TUMSSG). *Neurology* **51**: 765–772
Kantarci OH, Atkinson EJ, Hebrink DD *et al* 2000a Association of two variants in IL-1beta and IL-1 receptor antagonist genes with multiple sclerosis. *J Neuroimmunol* **106**: 220–227
Kantarci OH, Hebrink DD, Atkinson EJ e*t al* 2000b A comprehensive screen for genetic variation in the IFNgamma gene in multiple sclerosis. *Neurology* **56**: A95
Kantarci OH, Atkinson EJ, Hebrink DD *et al* 2000c Association of a myeloperoxidase promoter polymorphism with multiple sclerosis. *J Neuroimmunol* **105**: 189–194
Kantarci OH, de Andrade M, Weinshenker BG 2002 Identifying disease modifying genes in multiple sclerosis. *J Neuroimmunol* **123**: 144–159
Kantarci OH, Hebrink DD, Achenbach SJ *et al* 2003a CLTA4 is associated with susceptibility to multiple sclerosis. *J Neuroimmunol* **134**: 133–141
Kantarci OH, Schaefer-Klein JL, Hebrink DD *et al* 2003b A population-based study of IL4 polymorphisms in multiple sclerosis. *J Neuroimmunol* **137**: 134–139
Kantarci OH, Hebrink DD, Achenbach SJ *et al* 2004a Association of APOE polymorphisms with disease severity in MS is limited to women. *Neurology* **62**: 811–814
Kantarci OH, Hebrink DD, Achenbach SJ *et al* 2004b CD95 polymorphisms are associated with susceptibility to MS in women: a population-based study of CD95 and CD95L in MS. *J Neuroimmunol* **146**: 162–170
Kantarci OH, Goris A, Hebrink DD *et al* 2005 IFNG polymorphisms are associated with gender differences in susceptibility to multiple sclerosis. *Genes Immun* **6**: 153–161
Kanter DS, Horensky D, Sperling RA *et al* 1995 Plasmapheresis in fulminant acute disseminated encephalomyelitis. *Neurology* **45**: 824–827

Kantor AB, Herzenberg LA 1993 Origin of murine B cell lineages. *Ann Rev Immunol* **11**: 501–538

Kantor R, Bakhanashvili M, Achiron A 2003 A mutated CCR5 gene may have favourable prognostic implications in MS. *Neurology* **61**: 238–240

Kanwar JR, Harrison JEB, Wang D *et al* 2000 Beta7 integrins contribute to demyelinating disease of the central nervous system. *J Neuroimmunol* **103**: 146–152

Kanyerezi BR, Kiire CF, Obace A 1980 Multiple sclerosis in Mulago Hospital, Uganda. *East Afr Med J* **57**: 262–266

Kaplan EL, Meier P 1958 Non-parametric estimation from incomplete observations. *J Am Stat Assoc* **53**: 457–481

Kaplan MR, Meyer-Franke A, Lambert S *et al* 1997 Induction of sodium channel clustering by oligodendrocytes. *Nature* **386**: 724–728

Kaplan MR, Cho MH, Ullian EM *et al* 2001 Differential control of clustering of the sodium channels Na(v)1.2 and Na(v)1.6 at developing CNS nodes of Ranvier. *Neuron* **30**: 105–119

Kaplan SA, Reis RB, Kohn IJ *et al* 1999 Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction. *Urology* **53**: 481–486

Kaplanski G, Retornaz F, Durand J, Soubeyrand J 1995 Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype. *J Neurol Neurosurg Psychiatry* **58**: 758–759

Kaplin AI, Krishnan C, Deshpande DM *et al* 2005 Diagnosis and management of acute myelopathies. *Neurologist* **11**: 2–18

Kapoor R, Miller DH, Jones SJ *et al* 1988 Effects of intravenous methylprednisolone on outcome in MRI-based prognostic subgroups in acute optic neuritis. *Neurology* **50**: 230–237

Kapoor R, Brown P, Thompson PD, Miller DH 1992 Propriospinal myoclonus in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **55**: 1086–1088

Kapoor R, Smith KJ, Felts PA, Davies M 1993 Internodal potassium currents can generate ectopic impulses in mammalian myelinated axons. *Brain Res* **611**: 165–169

Kapoor R, Li YG, Smith KJ 1997 Slow sodium-dependent potential oscillations contribute to ectopic firing in mammalian demyelinated axons. *Brain* **120**: 647–652

Kapoor R, Miller DH, Jones SJ *et al* 1998 Effects of intravenous methylprednisolone on outcome in MRI based prognostic subgroups in acute optic neuritis. *Neurology* **50**: 230–237

Kapoor R, Davies M, Smith KJ 1999 Temporary axonal conduction block and axonal loss in inflammatory neurological disease: a potential role for nitric oxide? *Ann NY Acad Sci* **893**: 304–308

Kapoor R, Blaker PA, Hall SM *et al* 2000 Protection of axons from degeneration resulting from exposure to nitric oxide. *Rev Neurol (Paris)* **156**: 367

Kapoor R, Davies M, Blaker PA *et al* 2003 Blockers of sodium and calcium entry protect axons from nitric oxide-mediated degeneration. *Ann Neurol* **53**: 174–180

Kappos L, Duda P 2002 The Janus face of CNS-directed autoimmune response: a therapeutic challenge. *Brain* **125**: 2379–2380

Kappos L, Kesselring J 2003 Interferons in relapsing remitting multiple sclerosis. *Lancet* **361**:1821–2; author reply 1823–1824

Kappos L, Patzold U, Dommasch D *et al* 1988 Cyclosporine versus azathioprine in the long term treatment of multiple sclerosis – results of the German multicentre study. *Ann Neurol* 23: 56–63

Kappos L, Heun R, Mertens H-G 1990 A 10-year matched-pairs study comparing azathioprine and no immunosupppression in multiple sclerosis. *Eur Arch Psychiatry Clin Neurosci* **240**: 34–38

Kappos L, Radu EW, Haas J *et al* 1994 European multicenter trial of deoxyspergualin (DSG) versus placebo: results of the first interim analysis. *J Neurol* **241 (Suppl 1)**: S27

Kappos L, Moeri D, Radue EW *et al* 1999 Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. *Lancet* **353**: 964–969

Kappos L, Comi G, Panitch H *et al* 2000 Induction of a non-encephalitogenic type 2 T helper-cell autoimmune response in multiple sclerosis after administration of an altered peptide ligand in a placebo-controlled, randomized phase II trial. *Nature Med* **6**: 1176–1182

Kappos L, Polman C, Pozzilli C *et al* 2001 Final analysis of the European multicenter trial on IFNβ-1b in secondary-progressive MS. *Neurology* **57**: 1969–1975

Kappos L, Clanet M, Sandberg-Wollheim M *et al* 2005 Neutralizing antibodies and efficacy of interferon beta-1a: a 4-year controlled study. *Neurology* **65**: 40–47

Kara P, Friedlander MJ 1998 Dynamic modulation of cerebral cortex synaptic function by nitric oxide. *Prog Brain Res* **118**: 183–198

Karabudak R, Kurne A, Guc D *et al* 2004 Effect of interferon beta-1a on serum matrix metalloproteinase – 9(MMP-9) and tissue inhibitor of matrix metalloproteinase (TIMP-1) in relapsing remitting multiple sclerosis patients: one year follow-up results. *J Neurol* **251**: 279–283

Karacostas D, Christodoulou C, Drevelengas A *et al* 2002 Cytomegalovirus-associated transverse myelitis in a non-immunocompromised patient. *Spinal Cord* **40**: 145–149

Karandikar NJ, Vanderlugt CL, Walunas TL *et al* 1996 CTLA-4: a negative regulator of autoimmune disease. *J Exp Med* **184**: 783–788

Karandikar NJ, Crawford MP, Yan X *et al* 2002 Glatiramer acetate (Copaxone) therapy induces CD8(+) T cell responses in patients with multiple sclerosis. *J Clin Invest* **109**: 641–649

Karlsson J, Zhao X, Lonskaya I *et al* 2003 Novel quantitative trait loci controlling development of experimental autoimmune encephalomyelitis and proportion of lymphocyte subpopulations. *J Immunol* **170**: 1019–1026

Karnezis T, Mandemakers W, McQualter JL *et al* 2004 The neurite outgrowth inhibitor Nogo A is involved in autoimmune-mediated demyelination. *Nat Neurosci* **7**: 736–744

Karni A, Kohn Y, Safirman C *et al* 1999a Evidence for the genetic role of human leukocyte antigens in low frequency of DRB1*0501 multiple sclerosis patients in Israel. *Mult Scler* **5**: 410–415

Karni A, Bakimer-Kleiner R, Abramsky O, Ben-Nun A 1999b Elevated levels of antibody to myelin-oligodendrocyte glycoprotein is not specific for patients with multiple sclerosis. *Arch Neurol* **56**: 311–315

Karni A, Kahana E, Zilber N *et al* 2003 The frequency of multiple sclerosis in Jewish and Arab populations in greater Jerusalem. *Neuroepidemiology* **22**: 82–86

Karp CL, van Boxel-Dezaire AH, Byrnes AA, Nagelkerken L 2001 Interferon-beta in multiple sclerosis: altering the balance of interleukin-12 and interleukin-10? *Curr Opin Neurol* **14**: 361–368

Karpas A, Kampft U, Siden A *et al* 1986 Lack of evidence for involvement of known human retroviruses in multiple sclerosis. *Nature* **322**: 177–178

Karpus WJ, Lukacs NW, McRae BL *et al* 1995 An important role for the chemokine macrophage inflammatory protein-1a in the pathogenesis of the T cell-mediated autoimmune disease, experimental autoimmune encephalomyelitis. *J Immunol* **155**: 5003–5010

Karpusas M, Whitty A, Runkel L, Hochman P 1998 The structure of human interferon-beta: implications for activity. *Cell Mol Life Sci* **54**: 1203–1216

Kartje GL, Schulz MK, Lopez-Yunez A *et al* 1999 Corticostriatal plasticity is restricted by myelin-associated neurite growth inhibitors in the adult rat. *Ann Neurol* **45**: 778–786

Karussis DM, Leker RR, Ashkenazi A, Abramsky O 1998 A subgroup of multiple sclerosis patients with anticardiolipin antibodies and unusual clinical manifestations: do they represent a new nosological entity? *Ann Neurol* **44**: 629–634

Karussis DM, Meiner Z, Lehmann D *et al* 1996 Treatment of secondary progressive multiple sclerosis with the immunomodulator linomide: a double-blind, placebo-controlled pilot study with monthly magnetic resonance imaging evaluation. *Neurology* 47: 341–346

Kaspar A, Brinkmeier H, Rudel R 1994 Local anaesthetic-like effect of interleukin-2 on muscular Na+ channels: no evidence for involvement of the IL-2 receptor. *Pflugers Arch* **426**: 61–67

Kassiotis G, Pasparakis M, Kollias G, Probert L 1999 TNF accelerates the onset but does not alter the incidence and severity of myelin basic protein-induced experimental autoimmune encephalomyelitis. *Eur J Immunol* **29**: 774–780

Kassubek J, Tumani H, Ecker D *et al* 2003 Age-related brain parenchymal fraction is significantly decreased in young multiple sclerosis patients: a quantitative MRI study. *NeuroReport* **14**: 427–430

Kastenbauer S, Koedel U, Wick M *et al* 2003 CSF and serum levels of soluble fractalkine (CX3CL1) in inflammatory diseases of the nervous system. *J Neuroimmunol* **137**: 210–217

Kastrup O, Stude P, Limmroth V 2002 Balo's concentric sclerosis: evolution of active demyelination demonstrated by serial contrast-enhanced MRI. *J Neurol* **249**: 811–814

Katz D, Taubenberger JK, Cannella B *et al* 1993 Correlation between MRI findings and lesion development in chronic active multiple sclerosis. *Ann Neurol* **34**: 661–669

Katz JD, Ropper AH 2000 Progressive necrotic myelopathy: clinical course in 9 patients. *Arch Neurol* **57**: 355–361

Kaufman DL, Clare-Salzler M, Tian J *et al* 1993 Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. *Nature* **366**: 69–72

Kaufman JM, Fam B, Jacobs SC *et al* 1977 Bladder cancer and squamous metaplasia in spinal cord injury patients. *J Urology* **118**: 967–971

Kaufman M 1997 Treatment of multiple sclerosis with high-dose corticosteroids may prolong the prothrombin time to dangerous levels in patients taking warfarin. *Mult Scler* **3**: 248–249

Kaufman M, Gaydos CA, Sriram S *et al* 2002 Is *Chlamydia pneumoniae* found in spinal fluid samples from multiple sclerosis patients? Conflicting results. *Mult Scler* **8**: 289–294

Kaufmann SHE 1990 Heat shock proteins and the immune response. *Immunol Today* **11**: 129–136

Kaur C, Singh J, Lim MK *et al* 1995 The response of neurons and microglia to blast injury in the rat brain. *Neuropathol Appl Neurobiol* **21**: 369–377

Kawakami N, Lassmann S, Li Z *et al* 2004 The activation status of neuroantigen-specific T cells in the target organ determines the clinical outcome of autoimmune encephalomyelitis. *J Exp Med* **199**: 185–197

Kawakami N, Nägerl UV, Odoardi F *et al* 2005 Live imaging of effector cell trafficking and autoantigen recognition within the unfolding autoimmune encephalomyelitis lesion. *J Exp Med* **201**: 1805–1814

Kawamata T, Akiyama H, Yamada T, McGeer PL 1992 Immunologic reactions in amyotrophic lateral sclerosis brain and spinal cord. *Am J Pathol* **140**: 691–707

Kazarian EL, Gager WE 1978 Optic neuritis complicating measles, mumps, and rubella vaccination. *Am J Ophthalmol* **86**: 544–547

Kazarinova-Noyes K, Shrager P 2002 Molecular constituents of the node of Ranvier. *Mol Neurobiol* **26**: 167–182

Keane AH 1920 *Man Past and Present*. Cambridge: Cambridge University Press

Keane JR 1974 Periodic alternating nystagmus with downward beating nystagmus. *Arch Neurol* **30**: 399–402

Keane JR 2005 Internuclear ophthalmoplegia: unusual causes in 114 of 410 patients. *Arch Neurol* **62**: 714–717

Keegan M, Pineda AA, McClelland RL *et al* 2002 Plasma exchange for severe attacks of CNS demyelination: predictors of response. *Neurology* **58**: 143–146

Keegan M, Konig F, Bitsch A *et al* 2004 Multiple sclerosis pathological subtype predicts response to therapeutic plasma exchange. *Neurology* **62**: 259–260

Keirstead HS, Blakemore WF 1999 The role of oligodendrocytes and oligodendrocyte progenitors in CNS remyelination. *Adv Exp Med Biol* **468**: 183–197

Keitner JL, Johnson CA, Spurn JO, Beck RW, Optic Neuritis Study Group 1993 Baseline visual field profile of optic neuritis. *Arch Ophthalmol* **111**: 231–234

Keles MS, Taysi S, Sen N *et al* 2001 Effect of corticosteroid therapy on serum and CSF malondialdehyde and antioxidant proteins in multiple sclerosis. *Can J Neurol Sci* **28**: 141–143

Kellar-Wood H, Powys S, Gray J, Compston DAS 1994a MHC in coded TAP1 and TAP2 dimorphisms in multiple sclerosis. *Tissue Antigens* **43**: 129–132

Kellar-Wood H, Robertson N, Govan GG *et al* 1994b Leber's hereditary optic neuropathy mitochondrial DNA mutations in multiple sclerosis. *Ann Neurol* **36**: 109–112

Kellar-Wood H, Wood NW, Hoilmans P *et al* 1995 Multiple sclerosis and the HLA-D region: linkage and association studies. *J Neuroimmunol* **58**: 183–190

Keller G, Snodgrass HR 1999 Human embryonic stem cells: the future is now. *Nature Med* **5**: 151–152

Kelles A, Janssens J, Tack J 2000 IL-1beta and IL-6 excite neurones and suppress cholinergic neurotransmission in the myenteric plexus of the guinea pig. *Neurogastroenterol Motil* **12**: 531–538

Kelly BJ, Cronin M, Curran JJ 1989 Anticardiolipin syndrome resembling multiple sclerosis. *Arthritis Rheum* **32**: S71 (B126)

Kelly MA, Cavan DA, Penny MA *et al* 1993 The influence of HLA-DR and -DQ alleles on progression to multiple sclerosis following a clinically isolated syndrome. *Hum Immunol* **37**: 185–191

Kelly MA, Zhang Y, Penny MA *et al* 1995a Genetic susceptibility to multiple sclerosis in a Shanghai Chinese population. *Hum Immunol* **42**: 203–208

Kelly MA, Jacobs KH, Penny MA *et al* 1995b An investigation of HLA-encoded genetic susceptibility to multiple sclerosis in subjects of Asian Indian and Afro-Caribbean ethnic origin. *Tissue Antigens* **45**: 197–202

Kelly R 1985 In: Vinken PJ, Bruyn G, Klawans JHL (eds) *Handbook of Clinical Neurology*. Amsterdam: Elsevier, Vol 47, pp. 49–78

Kelsoe G 1996 Life and death in germinal centers (Redux). *Immunity* **4**: 107–111

Kemp K, Lion JR, Magram G 1977 Lithium in the case of a manic patient with multiple sclerosis: a case report. *Dis Nerv Syst* **38**: 210–211

Kenealy SJ, Babron MC, Bradford Y *et al* 2004 A second-generation genomic screen for multiple sclerosis. *Am J Hum Genet* **75**: 1070–1078

Kennedy C, Carroll FD 1960 Optic neuritis in children. *Arch Ophthalmol* **63**: 747–755

Kennedy C, Carter S 1961 Relation of optic neuritis to multiple sclerosis in children. *Pediatrics* **28**: 377–387

Kennedy MK, Torrance DS, Picha KS, Mohler KM 1992 Analysis of cytokine mRNA expression in the central nervous system of mice with experimental autoimmune encephalomyelitis reveals that IL-10 mRNA expression correlates with recovery. *J Immunol* **149**: 2496–2505

Kennedy PGE, Fok-Seang J 1986 Studies on the development, antigenic phenotype, and function of human glial cells in tissue culture. *Brain* **109**: 1261–1277

Kennedy PGE, Steiner I 1994 On the possible viral aetiology of multiple sclerosis. *Q J Med* **87**: 523–528

Kennedy PGE, Narayan O, Ghotbi Z *et al* 1985 Persistent expression of Ia antigen and viral genome in visna-maedi virus-induced inflammatory cells: possible role of lentivirus-induced interferon. *J Exp Med* **162**: 1970–1982

Kent-Braun JA, Sharma KR, Weiner MW, Miller RG 1994 Effects of exercise on muscle activation and metabolism in multiple sclerosis. *Muscle Nerve* **17**: 1162–1169

Kepes JJ 1993 Large focal tumor-like demyelinating lesions of the brain: intermediate entity between multiple sclerosis and acute disseminated encephalomyelitis? A study of 31 patients. *Ann Neurol* **33**: 18–27

Kerlero de Rosbo N, Bernard CC *et al* 1985 Concomitant detection of changes in myelin basic protein and permeability of blood-spinal cord barrier in acute experimental autoimmune encephalomyelitis by electroimmunoblotting. *J Neuroimmunol* **9**: 349–361

Kerlero de Rosbo N, Milo R, Lees MB *et al* 1993 Reactivity to myelin antigens in multiple sclerosis. *J Clin Invest* **92**: 2602–2608

Kerlero de Rosbo N, Mendel I, Ben-Nun A 1995 Chronic relapsing experimental autoimmune encephalomyelitis with a delayed onset and an atypical course, induced on PL/J mice by myelin

oligodendrocyte glycoprotein (MOG)-derived peptide: preliminary analysis of MOG T cell epitopes. *Eur J Immunol* **25**: 985–993

Kerlero de Rosbo N, Hoffman M *et al* 1997 Predominance of the autoimmune response to myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis: reactivity to the extracellular domain of MOG is directed against three main regions. *Eur J Immunol* **27**: 3059–3069

Kermode AG, Plant GT, MacManus DG *et al* 1989 Behçet's disease with slowly enlarging midbrain mass on MRI: resolution following steroid therapy. *Neurology* **39**: 1251–1252

Kermode AG, Thompson AJ, Tofts P *et al* 1990 Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis: pathogenetic and clinical implications. *Brain* **113**: 1477–1489

Keros S, McBain CJ 1997 Arachidonic acid inhibits transient potassium currents and broadens action potentials during electrographic seizures in hippocampal pyramidal and inhibitory interneurons. *J Neurosci* **17**: 3476–3487

Kerschensteiner M, Gallmeier E, Behrens L *et al* 1999 Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation? *J Exp Med* **189**: 865–870

Kerschensteiner M, Stadelmann C, Dechant G *et al* 2003 Neurotrophic cross-talk between the nervous and immune systems: implications for neurological diseases. *Ann Neurol* **53**: 292–304

Kersh EN, Shaw AS, Allen PM 1998 Fidelity of T cell activation through multistep T cell receptor zeta-phosphorylation. *Science* **281**: 572–575

Kerschensteiner M, Bareyre FM, Buddeberg BS *et al* 2004 Remodeling of axonal connections contributes to recovery in an animal model of multiple sclerosis 1. *J Exp Med* **200:** 1027–1038

Kessaris N, Jamen F, Rubin LL, Richardson WD 2004 Cooperation between sonic hedgehog and fibroblast growth factor/MAPK signalling pathways in neocortical precursors. *Development* **131**: 1289–1298

Kesselring J, Miller DH, MacManus DG *et al* 1989 Quantitative magnetic resonance imaging in multiple sclerosis: the effect of high dose intravenous methylprednisolone. *J Neurol Neurosurg Psychiatry* **52**: 14–17

Kesselring J, Miller DH, Robb SA *et al* 1990 Acute disseminated encephalomyelitis: magnetic resonance imaging findings and the distinction from multiple sclerosis. *Brain* **113**: 291–302

Khan AA, Bose C, Yam LS *et al* 2001 Physiological regulation of the immunological synapse by agrin. *Science* **292**, 1681–1686

Khan OA, Xia Q, Bever CT, Johnson KP, Panitch HS, Dhib-Jalbut SS 1996 Interferon beta-1b serum levels in multiple sclerosis following subcutaneous administration. *Neurology* **46**: 1639–1643

Khan OA, Bauserman SC, Rothman MI *et al* 1997 Concurrence of multiple sclerosis and brain tumor: clinical considerations. *Neurology* **48**: 1330–1333

Khan OA, Zvartau-Hind M, Caon C *et al* 2001a Effect of monthly intravenous cyclophosphamide in rapidly deteriorating multiple sclerosis patients resistant to conventional therapy. *Mult Scler* **7**: 185–188

Khan OA, Caon C, Zvartau-Hind M *et al* 2001b Clinical course and before and after change of immunomodulating therapy in relapsing–remitting MS. *Neurology* **56**: A355

Khan OA, Tselis AC, Kamholz JA *et al* 2001c A prospective, open-label treatment trial to compare the effect of IFNbeta-1a (Avonex), IFNbeta-1b (Betaseron), and glatiramer acetate (Copaxone) on the relapse rate in relapsing–remitting multiple sclerosis: results after 18 months of therapy. *Mult Scler* **7**: 349–353

Khan S, Yakub BA, Poser CM *et al* 1995 Multiphasic disseminated encephalomyelitis presenting as alternating hemiplegia. *J Neurol Neurosurg Psychiatry* **58**: 467–470

Khatri BO, McQuillen P, Harrington GJ *et al* 1985 Chronic progressive multiple sclerosis: double blind controlled trial of plasmapheresis in patients taking immunosuppressive treatment. *Neurology* **35**: 312–319

Khatri BO, McQuillen P, Hoffman RG 1991 Plasma exchange in chronic progressive multiple sclerosis: a long term study. *Neurology* **41**: 409–414

Kheradvar A, Tabassi AR, Nikbin B *et al* 2004 Influence of HLA on progression of optic neuritis to multiple sclerosis: results of a four-year follow-up study. *Mult Scler* **10**: 526–531

Khorchid A, Fragoso G, Shore G, Almazan G 2002 Catecholamine-induced oligodendrocyte cell death in culture is developmentally regulated and involves free radical generation and differential activation of caspase-3. *Glia* **40**: 283–299

Khoury SJ, Hancock WW, Weiner HL 1992 Oral tolerance to myelin basic protein and natural recovery from experimental autoimmune encephalomyelitis are associated with downregulation of inflammatory cytokines and differential upregulation of transforming growth factor β, interleukin 4, and prostaglandin E expression in the brain. *J Exp Med* **176**: 1355–1364

Khoury SJ, Akalin E, Chandraker A *et al* 1995 CD28-B7 costimulatory blockade by CTLA4Ig prevents actively induced experimental autoimmune encephalomyelitis and inhibits Th1 but spares Th2 cytokines in the central nervous system. *J Immunol* **155**: 4521–4524

Khun P, Steiner G 1917 Über die Ursache der multiplen Sklerose. *Med Klin* **13**: 1007–1014

Kibler RF, Fritz RB, Chou FC-H *et al* 1977 Immune response of Lewis rats to peptide C1 (residues 68–88) of guinea pig and rat myelin basic proteins. *J Exp Med* **146**: 1323–1331

Kidd D, Thompson AJ 1997 Prospective study of neurorehabilitation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **62**: 423–424

Kidd D, Thorpe JW, Thompson *et al* 1993 Spinal cord MRI using multi-array coils and fast spin echo. II: Findings in multiple sclerosis. *Neurology* **43**: 2632–2637

Kidd D, Thompson AJ, Kendall BE *et al* 1994 Benign form of multiple sclerosis: MRI evidence for less frequent and less inflammatory disease activity. *J Neurol Neurosurg Psychiatry* **57**: 1070–1072

Kidd D, Thorpe JW, Kendall BE *et al* 1996 MRI dynamics of brain and spinal cord in progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* **60**: 15–19

Kidd D, Thompson PD, Day BL *et al* 1998 Central motor conduction time in progressive multiple sclerosis: correlations with MRI and disease activity. *Brain* **121**: 1109–1116

Kidd D, Barkhof F, McConnell R *et al* 1999a Cortical lesions in multiple sclerosis. *Brain* **122**: 17–26

Kidd D, Steuer A, Denman AM, Rudge P 1999b Neurological complications in Behcet's syndrome. *Brain* **122**: 2183–2194

Kidd D, Burton B, Plant GT, Graham EM 2003 Chronic relapsing inflammatory optic neuropathy (CRION). *Brain* **126**: 278–284

Kiernan BW, ffrench Constant C 1993 Oligodendrocyte precursor (O-2A progenitor cell) migration: a model system for the study of cell migration in the developing central nervous system. *Development* **119 (Suppl)**: S219–S225

Kiernan MC, Hales JP, Gracies JM *et al* 1997 Paraesthesiae induced by prolonged high frequency stimulation of human cutaneous afferents. *J Physiology* **501**: 461–471

Kiernan MC, Lin CS, Andersen KV *et al* 2001 Clinical evaluation of excitability measures in sensory nerve. *Muscle Nerve* **24**: 883–892

Kiernan MC, Guglielmi JM, Kaji R *et al* 2002 Evidence for axonal membrane hyperpolarization in multifocal motor neuropathy with conduction block. *Brain* **125**: 664–675

Kierstead HS, Levine JM, Blakemore WF 1998 Response of the oligodendrocyte progenitor cell population (defined by NG2 labelling) to demyelination of the adult spinal cord. *Glia* **22**: 161–170

Kies B 1989 An epidemiological study of multiple sclerosis in Cape Town, South Africa. *XIVth World Congress of Neurology, New Delhi, India*, abstract 612B05

Kies MW, Murphy JB, Alvord EC 1960 Fractionation of guinea pig brain proteins with encephalitogenic activity. *Federation Proc (Bethesda)* **19**: 207

Kies MW, Alvord EC Jr, Martenson RE, LeBaron FN 1966 Encephalitogenic activity of bovine basic proteins. *Science* **151**: 821–822

Kikuchi S, Fukazawa T, Niino M *et al* 2002a Estrogen receptor gene polymorphism and

multiple sclerosis in Japanese patients: interaction with HLA-DRB1*1501 and disease modulation. *J Neuroimmunol* **128**: 77–81

Kikuchi S, Niino M, Fukazawa T *et al* 2002b An assessment of the association between IL-2 gene polymorphisms and Japanese patients with multiple sclerosis. *J Neurol Sci* **205**: 47–50

Kikuchi S, Fukazawa T, Niino M *et al* 2003 HLA-related subpopulations of MS in Japanese with and without oligoclonal bands. *Neurology* **60**: 647–651

Kilbinger H 1996 Modulation of acetylcholine release by nitric oxide. *Prog Brain Res* **109**: 219–224

Killestein J, Hoogervorst EL, Reif M *et al* 2002a Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* **58**: 1404–1407

Killestein J, Olsson T, Wallstrom E *et al* 2002b Antibody-mediated suppression of Vbeta5.2/5.3(+) T cells in multiple sclerosis: results from an MRI-monitored phase II clinical trial. *Ann Neurol* **51**: 467–474

Killestein J, Rep MHG, Meilof JF *et al* 2002c Seasonal variation in immune measurements and MRI markers of disease activity in MS. *Neurology* **58**: 1077–1080

Killestein J, Hoogervorst EL, Reif M *et al* 2003 Immunomodulatory effects of orally administered cannabinoids in multiple sclerosis. *J Neuroimmunol* **137**: 140–143

Killian JM, Bressler RB, Armstrong RM, Huston DP 1988 Controlled pilot trial of monthly intravenous cyclophosphamide in multiple sclerosis. *Arch Neurol* **45**: 27–30

Kim G, Tanuma N, Kojima T *et al* 1998 CDR3 size spectratyping and sequencing of spectratype-derived TCR of spinal cord T cells in autoimmune encephalomyelitis. *J Immunol* **160**: 509–513

Kim HJ, Ifergan I, Antel J *et al* 2004 Type-2 monocyte and microglia differentiation mediated by glatiramer acetate therapy in patients with multiple sclerosis. *J Neuroimmunol* **172**: 7144–7153

Kim JH, Auerbach JM, Rodriguez-Gomez JA *et al* 2002 Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature* **418**: 50–56

Kim JH, Lee SI, Park SI, Yoo WH 2003 Recurrent transverse myelitis in primary antiphospholipid syndrome: case report and literature review. *Rheumatol Int* **24**: 244–246

Kim JY, Sun Q, Oglesbee M, Yoon SO 2003 The role of ErbB2 signaling in the onset of terminal differentiation of oligodendrocytes in vivo. *J Neurosci* **23**: 5561–5571

Kim KK 2003 Idiopathic recurrent transverse myelitis. *Arch Neurol* **60**: 1290–1294

Kim SU, Murray MR, Tourtellotte WW 1970 Demonstration in tissue culture of myelino-toxicity in cerebrospinal fluid and brain extracts from multiple sclerosis patients. *J Neuropathol Exp Neurol* **29**: 420–431

Kim SU, McMorris FA, Sprinkle T 1984 Immunofluorescence demonstration of 2',3'-cyclic nucleotide phosphodiesterase in cultured oligodendrocytes of mouse, rat, calf and human. *Brain Res* **300**: 195–199

Kim YS, Kim SU 1991 Oligodendroglial cell death induced by oxygen radicals and its protection by catalase. *J Neurosci Res* **29**: 100–106

Kimiskidis V, Tsimourtou VSP *et al* 2002 Autologous stem cell transplantation in multiple sclerosis: the MRI study. *J Neurol* **249**: I61

Kimura K, Hunter SF, Thollander MS *et al* 2000 Concurrence of inflammatory bowel disease and multiple sclerosis. *Mayo Clin Proc* **75**: 802–806

Kinlen LJ 1985 Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am J Med* **78**: 44–49

Kinnman J, Link H 1984 Intrathecal production of oligoclonal IgM and IgG in CNS sarcoid. *Acta Neurol Scand* **69**: 97–106

Kinnunen E 1983 The incidence of optic neuritis and its prognosis for multiple sclerosis. *Acta Neurol Scand* **68**: 371–377

Kinnunen E 1984 Multiple sclerosis in Finland: evidence of increasing frequency and uneven geographic distribution. *Neurology* **34**: 457–461

Kinnunen E, Wikström J 1986 Prevalence and prognosis of epilepsy in patients with multiple sclerosis. *Epilepsia* **27**: 729–733

Kinnunen E, Koskenvuo M, Kaprio J, Aho K 1987 Multiple sclerosis in a nationwide series of twins. *Neurology* **37**: 1627–1629

Kinnunen E, Juntunen J, Ketonen L *et al* 1988 Genetic susceptibility to multiple sclerosis: a co-twin study of a nation-wide series. *Arch Neurol* **45**: 1108–1111

Kinnunen E, Müller K, Keto P *et al* 1993 Cerebrospinal fluid and MRI findings in three patients with multiple sclerosis and systemic lupus erythematosus. *Acta Neurol Scand* **87**: 356–360

Kioy PG 2001 Emerging picture of multiple sclerosis in Kenya. *East Afr Med J* **78**: 93–96

Kipnis J, Yoles E, Cohen A *et al* 2000 T cell immunity to copolymer 1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. *Proc Natl Acad Sci USA* **97**: 7446–7451

Kira JI 2003 Multiple sclerosis in the Japanese population. *Lancet Neurol* **2**: 117–126

Kira JI, Kanai T, Nishimura Y *et al* 1996 Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders. *Ann Neurol* **40**: 569–574

Kira JI, Yamasaki K, Horiuchi I *et al* 1999 Changes in the clinical phenotypes of multiple sclerosis during the past 50 years in Japan. *J Neurol Sci* **166**: 53–57

Kirk CW, Droogan AG, Hawkins SA *et al* 1997 Tumour necrosis factor microsatellites show association with multiple sclerosis. *J Neurol Sci* **147**: 21–25

Kirk CW, Graham CA, McDonnell GV, Hawkins SA 2000 Chromosome 10 locus apolipoprotein C-11 association with multiple sclerosis. *Mult Scler* **6**: 291–292

Kirk J 1979 The fine structure of the CNS in multiple sclerosis: vesicular demyelination in an acute case. *Neuropathol Appl Neurobiol* **5**: 289–294

Kirk J, Hutchinson WM 1978 The fine structure of the CNS in multiple sclerosis: interpretation of cytoplasma papovavirus-like and paramyxovirus-like inclusions. *Neuropathol Appl Neurobiol* **4**: 343–356

Kirk PF, Compston DAS 1990 The effect of methylprednisolone on lymphocyte phenotype and function in patients with multiple sclerosis. *J Neuroimmunol* **26**: 1–8

Kirk PF, Williams J, Petersen M, Compston DAS 1994 The effect of methylprednisolone on monocyte eicosanoid production in patients with multiple sclerosis. *J Neurol* **241**: 427–431

Kirkpatrick JB, Hayman LA 1987 White matter lesions in MR imaging of clinically healthy brains of elderly subjects: possible pathological basis. *Radiology* **162**: 509–511

Kiss JP, Vizi ES 2001 Nitric oxide: a novel link between synaptic and nonsynaptic transmission. *Trends Neurosci* **24**: 211–215

Kivisäkk P, Alm GV, Tian WZ *et al* 1997 Neutralising and binding anti-interferon-β-1b treatment of multiple sclerosis. *Mult Scler* **3**: 184–190

Kivisäkk P, Tian W, Matusevicius D *et al* 1998a Optic neuritis and cytokines: no relation to MRI abnormalities and oligoclonal bands. *Neurology* **50**: 217–223

Kivisäkk P, Matusevicius D, He B *et al* 1998b IL-15 mRNA expression is up-regulated in blood and cerebrospinal fluid mononuclear cells in multiple sclerosis (MS). *Clin Exp Immunol* **111**: 193–197

Kivisäkk P, Lundahl, J, von Heigl Z, Fredrikson S 1998c No evidence for increased frequency of autoantibodies during interferon-beta1b treatment of multiple sclerosis. *Acta Neurol Scand* **97:** 320–323

Kivisäkk P, Trebst C, Liu Z *et al* 2002 T-cells in the cerebrospinal fluid express a similar repertoire of inflammatory chemokine receptors in the absence or presence of CNS inflammation: implications for CNS trafficking. *Clin Exp Immunol* **129**: 510–518

Kivisäkk P, Mahad D, Callahan MK *et al* 2003 Human cerebrospinal fluid central memory CD4+ T cells: evidence for trafficking through choroid plexus and meninges via P-selectin. *Proc Natl Acad Sci USA* **100**: 8389–8394

Klapper JA 1994 Interferon beta treatment of multiple sclerosis. *Neurology* **44**: 188; author reply 188–190

Klausner I 1901 Ein Beitrag zür Aetiologie der multiplen Sklerose. *Arch Psychiat* **34**: 841–869

Kleijnen J, Knipschild P 1995 Hyperbaric oxygen for multiple sclerosis: review of controlled trials. *Acta Neurol Scand* **91**: 330–334

Klein GM, Rose MS, Seland TP 1994 A prevalence study of multiple sclerosis in the

Crowsnest Pass region of southern Alberta. *Can J Neurol Sci* **21**: 262–265
Klein L, Klugmann M, Nave K-A *et al* 2000 Shaping of the autoreactive T cell repertoire by a splice variant of self protein expressed in thymic epithelial cells. *Nature Med* **6**: 56–61
Klein RS, Izikson L, Means T *et al* 2004 IFN-inducible protein 10/CXC chemokine ligand 10-independent induction of experimental autoimmune encephalomyelitis. *J Immunol* **112**: 550–559
Kleine TO, Albrecht J, Zofel F 1999 Flow cytometry of cerebrospinal fluid (CSF) lymphocytes: alterations of blood/CSF ratios of lymphocyte subsets in inflammatory disorders of the human central nervous system. *Clin Chem Lab Med* **37**: 231–241
Kleinman M, Brunquell P 1995 Acute disseminated encephalomyelitis: response to intravenous immunoglobulin? *J Child Neurol* **10**: 481–483
Kleinschmidt-Demasters BK, Tyler KL 2005 Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* **353**: 369–374
Kleyweg RP, van der Meche FG, Meulstee J 1988 Treatment of Guillain-Barre syndrome with high-dose gammaglobulin. *Neurology* **38**: 1639–1641
Klie LB, Margulies SL, Oh SJ 1982 Optic neuritis and myelitis following rubella vaccination. *Arch Neurol* **39**: 443–444
Klitz W, Maiers M, Spellman S *et al* 2003 New HLA haplotype frequency reference standards: high-resolution and large sample typing of HLA DR-DQ haplotypes in a sample of European Americans. *Tissue Antigens* **62**: 296–307
Klostermann W, Vieregge P, Köpf D 1993 Spamodic torticollis in multiple sclerosis: significance of an upper cervical spinal cord lesion. *Mov Disord* **8**: 234–236
van der Knaap MAA, Kamphorst W, Barth PG *et al* 1998 Phenotypic variation in leucoencephalopathy with vanishing white matter. *Neurology* **51**: 540–547
van der Knaap MAA, Leegwater PAJ, Konst AAM *et al* 2002 Mutations in each of the 5 subunits of translation initiation factor eIF2B can cause leucoencephalopathy with vanishing white matter. *Ann Neurol* **51**: 264–270
van der Knaap MS, Valk J 1995 *Magnetic Resonance of Myelin, Myelination and Myelin Disorders*. Berlin: Springer
Knobler RL, Panitch HS, Braheny JC *et al* 1984 Systemic alpha interferon therapy of multiple sclerosis. *Neurology* **34**: 1273–1279
Knox KK, Brewer JH, Henry JM *et al* 2000 Human herpesvirus 6 and multiple sclerosis: systemic active infections in patients with early disease. *Clin Infect Dis* **31**: 894–903
Kobayashi K, Kobayashi H, Ueda M, Honda Y 1996 Monoclonal antibody, KK1, recognises human retinal astrocytes and distinguishes a sub-type of astrocyte in mouse brain. *Brain Res* **740**: 57–65
Koch MJ, Reed D, Stern R, Brody JA 1974 Multiple sclerosis: a cluster in a small northwestern United States community. *J Am Med Assoc* **228**: 1555–1557
Koch-Henriksen N 1989 An epidemiological study of multiple sclerosis: familial aggregation, social determinants and exogenous factors. *Acta Neurol Scand* **80 (Suppl 124)**: 123
Koch-Henriksen N 1995 Multiple sclerosis in Scandinavia and Finland. *Acta Neurol Scand suppl* **161**: 55–59
Koch-Henriksen N 1999 The Danish multiple sclerosis register: a 50-year follow-up. *Mult Scler* **5**: 293–296
Koch-Henriksen N, Bronnum-Hansen H, Hyllested K 1992 Incidence of multiple sclerosis in Denmark 1948–1982: a descriptive nationwide study. *Neuroepidemiology* **11**: 1–10
Koch-Henriksen N, Bronnum-Hansen H, Hyllested K 1994 The Danish multiple sclerosis registry: a 44 year review. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 79–86
Koch-Henriksen N, Bronnum-Hansen H, Stenager E 1998 Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis registry. *J Neurol Neurosurg Psych* **65**: 56–59
Koh CS, Gausas J, Paterson PY 1993 Neurovascular permeability and fibrin deposition in the central nervous system of Lewis rats with cell-transferred experimental allergic encephalomyelitis in relationship to clinical and histopathological features of the disease. *J Neuroimmunol* **47**: 141–146
Koh D-R, Fung-Leung W-P, Ho A *et al* 1992 Less mortality but more relapses in experimental allergic encephalomyelitis in $CD8^{-/-}$ mice. *Science* **256**: 1210–1213
Kohama I, Lankford KL, Preiningerova J *et al* 2001 Transplantation of cryopreserved adult human Schwann cells enhances axonal conduction in demyelinated spinal cord. *J Neurosci* **21**: 944–950
Kohji T, Matsumoto Y 2000 Coexpression of Fas/FasL and Bax on brain and infiltrating T cells in the central nervous system is closely associated with apoptotic cell death during autoimmune encephalomyelitis. *J Neuroimmunol* **106**: 165–171
Kohler J, Kasper J, Kern U, Thoden U, Rehse-Küpper B 1986 Borrelia encephalomyelitis. *Lancet* **ii**: 35
Koibuchi T, Nakamura T, Miura T *et al* Acute disseminated encephalomyelitis following *Plasmodium vivax* malaria. *J Infect Chemother* **9**: 254–256
Koike F, Satoh J-I, Miyake S *et al* 2003 Microarray analysis identifies interferon beta regulated genes in multiple sclerosis. *J Neuroimmunol* **139**: 109–118
Kojima A, Tanaka-Kojima Y, Sakakura T, Nishizuka Y 1976 Prevention of post-thymectomy autoimmune thyroiditis in mice. *Lab Invest* **34**: 601–605
Kojima K, Berger Th, Lassmann H *et al* 1994 Experimental autoimmune panencephalitis and uveoretinitis transfered to the Lewis rat by T-lymphocytes specific for the S100β molecule, a calcium binding protein of astroglia. *J Exp Med* **180**: 817–829
Kojima K, Lassmann H, Wekerle H, Linington C 1997 The thymus and self tolerance: co-existence of encephalitogenic S-100 beta-specific T cells and their nominal autoantigen, in the normal adult rat thymus. *Int Immunol* **9**: 897–904
Kolb SJ, Costello F, Lee AG *et al* 2003 Distinguishing ischaemic stroke from the stroke-like lesions of MELAS using apparent diffusion coefficient mapping. *J Neurol Sci* **216**: 11–15
Koldovsky V, Koldovsky P, Henle G, Henle W, Ackerman R, Haase G 1975 Multiple sclerosis-associated agent: transmission to animals and some properties of the agent. *Infect Immunol* **12**: 1355–1366
Koles AJ, Rasminsky M 1972 A computer simulation of conduction in demyelinated nerve fibres. *J Physiol* **227**: 351–364
Köller H, Siebler M, Pekel M, Müller HW 1993 Depolarization of cultured astrocytes by leukotriene B_4: evidence for the induction of a K^+ concuctance inhibitor. *Brain Res* **612**: 28–44
Köller H, Thiem K, Siebler M 1996 Tumour necrosis factor-alpha increases intracellular Ca2+ and induces a depolarization in cultured astroglial cells. *Brain* **119**: 2021–2027
Köller H, Siebler M, Hartung H-P 1997 Immunologically induced electrophysiological dysfunction: implications for inflammatory diseases of the CNS and PNS. *Progr Neurobiol* **52**: 1–26
Köller H, Allert N, Oel D *et al* 1998 TNF alpha induces a protein kinase C-dependent reduction in astroglial K+ conductance. *NeuroReport* **9**: 1375–1378
Komoly S, Hudson LD, Webster HD, Bondy CA 1992 Insulin-like growth factor I gene expression is induced in astrocytes during experimental demyelination. *Proc Natl Acad Sci USA* **89**: 1894–1898
Koncan-Vracko B 1994 Epidemiological investigations of multiple sclerosis in Slovenia. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 294
Kondo T, Raff M 2000 Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. *Science* **289**: 1754–1757
Kondo T, Raff MC 2004 A role for Noggin in the development of oligodendrocyte precursor cells. *Dev Biol* **267**: 242–251
Kondo T, Yamamura T, Inobe J-I *et al* 1996 TCR repertoire to proteolipid protein (PLP) in

multiple sclerosis (MS): homologies between PLP-specific T cells and MS associated T cells in TCR junctional sequences. *Int Immunol* **8**: 123–130

Konno H, Yamamoto T, Suzuki H *et al* 1990 Targeting of adoptively transferred experimental allergic encephalomyelitis lesion at the site of Wallerian degeneration. *Acta Neuropathol* **80**: 521–526

Koprowski H, De Freitas EC, Harper ME *et al* 1985 Multiple sclerosis and human T-cell lymphotrophic retroviruses. *Nature* **318**: 154–160

Kornek B, Lassmann H 1999 Axonal pathology in multiple sclerosis: a historical note. *Brain Pathol* **9**: 651–656

Kornek B, Storch M, Weissert R *et al* 2000 Multiple sclerosis and chronic autoimmune encephalomyelitis: a comparative quantitative study of axonal injury in active, inactive and remyelinated lesions. *Am J Pathol* **157**: 267–276

Kornek B, Storch MK, Bauer J *et al* 2001 Distribution of calcium channel subunit in dystrophic axons in multiple sclerosis and experiemntal autoimmune encephalomyelitis. *Brain* **124**: 1114–1124

Körner H, Lemckert FA, Chaudhri G *et al* 1997 Tumor necrosis factor blockade in actively induced experimental autoimmune encephalomyelitis prevents clinical disease despite activated T cell infiltration to the central nervous system. *Eur J Immunol* **27**: 1973–1981

Kornhuber HH, Schutz A 1990 Efficient treatment of neurogenic bladder disorders in multiple sclerosis with initial intermittent catheterisation and ultrasound-controlled training. *Eur Neurol* **30**: 260–267

Korn-Lubetzki I, Kahana E, Cooper G, Abramsky O 1984 Activity of multiple sclerosis during pregnancy and puerperium. *Ann Neurol* **16**: 229–231

Kotter MR, Setzu A, Sim FJ *et al* 2001 Macrophage depletion impairs oligodendrocyte remyelination following lysolecithin-induced demyelination. *Glia* **35**: 204–212

Kotzin BL, Karuturi S, Chou YK *et al* 1991 Preferential T-cell receptor β-chain variable gene use in myelin basic protein-reactive T-cell clones from patients with multiple sclerosis. *Proc Natl Acad Sci USA* **88**: 9161–9165

Koudriavtseva T, Thompson AJ, Fiorelli M *et al* 1997 Gadolinium enhanced MRI predicts clinical and MRI disease activity in relapsing–remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* **62**: 285–287

Kovacs GG, Hoeftberger R, Majtenyi K *et al* 2005 Neuropathology of white matter disease in Leber's hereditary optic neuropathy associated with the T14484C mutation. *Brain* **128**: 35–41

Kowalzick L 1997 Psoriasis flare caused by recombinant interferon beta injections. *J Am Acad Dermatol* **36**: 501

Kozak T, Havrdova E, Pitha J *et al* 2002 Immunoablative therapy with PBPC support with in vitro or in vivo T-cell depletion in patients with poor risk multiple sclerosis. *Bone Marrow Transplantation* **29**: S15

Kozin F, Haughton V, Bernhard GC 1977 Neuro-Behçet-disease: two cases and neuroradiologic findings. *Neurology* **17**: 1148–1152

Koziol JA, Feng AC 2004 Seasonal variations in exacerbations and MRI parameters in relapsing–remitting multiple sclerosis. *Neuroepidemiology* **23**: 217–223

Kozlowski PB, Schuller-Levis GB, Wisniewski HM 1987 Induction of synchronized relapses in SJL/J mice with chronic relapsing experimental allergic encephalomyelitis. *Acta Neuropathol* **74**: 163–168

Kozovska ME, Hong J, Zang YC *et al* 1999 Interferon beta induces T-helper 2 immune deviation in MS. *Neurology* **53**: 1692–1697

Kraft GH 1998 Rehabilitation principles for patients with multiple sclerosis. *J Spinal Cord Med* **21**: 117–120

Kraft GH, Freal JE, Coryell JK *et al* 1981 Multiple sclerosis: early prognostic guidelines. *Arch Phys Med Rehab* **62**: 54–58

Krakowski M, Owens T 1996 Interferon-gamma confers resistance to experimental allergic encephalomyelitis. *Eur J Immunol* **26**: 1641–1646

Krakowski ML, Owens T 2000 Naive T lymphocytes traffic to inflamed central nervous system, but require antigen recognition for activation. *Eur J Immunol* **30**: 1002–1009

Kral MG, Xiong Z, Study RE 1999 Alteration of Na+ currents in dorsal root ganglion neurons from rats with a painful neuropathy. *Pain* **81**: 15–24

Kramer R, Zhang Y, Gehrmann J *et al* 1995 Gene transfer through the blood-nerve barrier: nerve growth factor engineered neuritogenic T lymphocytes attenuate experimental autoimmune neuritis. *Nature Med* **1**: 1162–1166

Krametter D, Niederweiser G, Berghold A *et al* 2001 *Chlamydia pneumoniae* in multiple sclerosis: humoral immune responses in serum and cerebrospinal fluid and correlation with disease activity marker. *Mult Scler* **7**: 13–18

Kranz JMS, Kurland LT, Schuman LM, Layton D 1983 Multiple sclerosis in Olmsted and Mower Counties, Minnesota. *Neuroepidemiology* 2: 206–218

Kraus J, Oschmann P, Engelhardt B *et al* 2000a CD45RA+ ICAM3+ lymphocytes in cerebrospinal fluid and blood as markers of disease activity in patients with multiple sclerosis. *Acta Neurol Scand* **102**: 326–332

Kraus J, Oschmann P, Engelhardt B *et al* 2000b Soluble and cell surface ICAM-3 in blood and cerebrospinal fluid of patients with multiple sclerosis: influence of methylprednisolone treatment and relevance as markers for disease activity. *Acta Neurol Scand* **101**: 135–139

Krauscher MF, Miller EM 1982 Central serous choroidoretinopathy misdiagnosed as a manifestation of multiple sclerosis. *Ann Ophthalmol* **14**: 215–218

Kreisler A, De Sèze J, Stojkovic T *et al* 2003 Multiple sclerosis, interferon beta, and clinical thyroid dysfunction. *Acta Neurol Scand* **107**: 154–157

Krellmann H 1980 Egk, Werner In: Sadie S (ed.) *New Grove Dictionary of Music and Musicians*. London: Macmillan, Vol 6, p. 68

Kremenchutzky M, Cottrell D, Rice G *et al* 1999 The natural history of multiple sclerosis: a geographically based study 7. Progressive-relapsing and relapsing-progressive multiple sclerosis: a re-evaluation. *Brain* **122**: 1941–1949

Kriesel JD, White A, Hayden F *et al* 2004 Multiple sclerosis attacks are associated with picornavirus infections. *Mult Scler* **10**: 145–148

Krishnan C, Kerr DA 2005 Idiopathic transverse myelitis. *Arch Neurol* **62:** 1011–1013

Kriss A, Francis DA, Cuendet F *et al* 1988 Recovery after optic neuritis in childhood. *J Neurol Neurosurg Psychiatry* **51**: 1253–1258

Kroencke DC, Lynch SG, Denney DR 2000 Fatigue in multiple sclerosis: relationship to depression, disability, and disease pattern. *Mult Scler* **6**: 131–136

Kroepfl JF, Viise LR, Charron AJ *et al* 1996 Investigation of myelin/oligodendrocyte glycoprotein membrane topology. *J Neurochem* **67**: 2219–2122

Kroner A, Mehling M, Hemmer B *et al* 2005a A PD-1 polymorphism is associated with disease progression in multiple sclerosis. *Ann Neurol* **58**: 50–57

Kroner A, Vogel F, Kolb-Mäurer *et al* 2005b Impact of the Asp299Gly polymorphism in the toll-like receptor 4 (*TLR4*) gene on disease course of multiple sclerosis. *J Neuroimmunol* **165**: 161–165

Krücke W 1973 On the histopathology of acute hemorrhagic leucoencephalitis, acute disseminated encephalitis and concentric sclerosis. In: Shiraki H, Yonezawa T, Kuroiwa Y (eds) *International Symposium on Aetiology and Pathogenesis of the Demyelinating Diseases*, Kyoto, pp. 1–27

Kruglyak L 1999 Prospects for whole-genome linkage disequilibrium mapping of common disease genes. *Nature Genetics* **22**: 139–144

Kruglyak L, Lander ES 1995 Complete multipoint sib-pair analysis of qualitative and quantitative traits. *Am J Hum Genet* **57**: 439–454

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES 1996 Parametric and nonparametric linkage analysis: a unified multipoint approach. *Am J Hum Genet* **58**: 1347–1363

Krumbholz M, Theil D, Derfuss T *et al* 2005 BAFF is produced by astrocytes and upregulated in multiple sclerosis lesions and

primary central nervous system lymphoma. *J Exp Med* **201**: 195–200
Krupp LB 2003 Fatigue in multiple sclerosis: definition, pathophysiology and treatment. *CNS Drugs* **17**: 225–234
Krupp LB, Elkins LE 2000 Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology* **55**: 934–939
Krupp LB, Pollina DA 1996 Mechanisms and management of fatigue in progressive neurological disorders. *Curr Opin Neurol* **9**: 456–460
Krupp LB, Rizvi SA 2002 Symptomatic therapy for underrecognized manifestations of multiple sclerosis. *Neurology* **58**: S32–S39
Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC 1988 Fatigue in multiple sclerosis. *Arch Neurol* **45**: 435–437
Krupp LB, Coyle PK, Doscher C *et al* 1995 Fatigue therapy in multiple sclerosis: results of a double-blind, randomised, parallel trial of amantidine, pemoline and placebo. *Neurology* **45**: 1956–1961
Krupp LB, Christodoulou C, Melville P *et al* 2004a Effects of donepezil on memory and cognition in multiple sclerosis: comprehensive analysis of the AIMS Study. *Neurology* **62**: A179–A180
Krupp LB, Christodoulou C, Melville P *et al* 2004b Donepezil improved memory in multiple sclerosis in a randomized clinical trial. *Neurology* **63**: 1579–1585
Ksiazek SM, Repka MX, Maguire A *et al* 1989 Divisional oculomotor nerve paresis caused by intrinsic brainstem disease. *Ann Neurol* **26**: 714–718
Ku B, Lee K 1998 Acute transverse myelitis caused by Coxsackie virus B4 infection: a case report. *J Korean Med Sci* **13**: 449–453
Kubes P, Suzuki M, Granger DN 1991 Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci USA* **88**: 4651–4655
Kuchroo VK, Sobel RA, Laning JC *et al* 1992 Experimental allergic encephalomyelitis mediated by cloned T cells specific for a synthetic peptide of myelin proteolipid protein: fine specificity and T cell receptor Vβ usage. *J Immunol* **148**: 3776–3782
Kuhlmann T, Glas M, zum Bruch C *et al* 2002a Investigation of bax, bcl-2, bcl-x and p53 gene polymorphisms in multiple sclerosis. *J Neuroimmunol* **129**: 154–160
Kuhlmann T, Lingfield G, Bitsch A *et al* 2002b Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. *Brain* **125**: 2202–2212
Kujala P, Portin R, Ruutianen J 1997 The progress of cognitive decline in multiple sclerosis: a controlled 3-year follow-up. *Brain* **120**: 289–297
Kukekov VG, Laywell ED, Suslov ON *et al* 1999 Multipotent stem/progenitor cells with similar properties arise from two neurogenic regions of adult human brain. *Exp Neurol* **156**: 333–344
Kuker W, Nagële T, Korfel A *et al* 2005 Primary central nervous system lymphoma (PCNSL): MRI features at presentation in 100 patients. *J Neuro-oncol* **72**:169–77
Kumar N, Low PA 2004 Myeloneuropathy and anaemia due to copper malabsorption. *J Neurol* **251**: 747–749
Kumar N, McEvoy KM, Ahlskog JE 2003 Myelopathy due to copper deficiency following gastric surgery. *Arch Neurol* **60**: 1782–1785
Kumar N, Gross JB jr, Ahlskog JE 2004 Copper deficiency myelopathy produces a picture like subacute combined degeneration. *Neurology* **63**: 33–39
Kunkel EJ, Butcher EC 2002 Chemokines and the tissue-specific migration of lymphocytes. *Immunity* **16**: 1–4
Kuokkanen S, Sundvall M, Terwilliger JD *et al* 1996 A putative vulnerability locus to multiple sclerosis maps to 5p14-p12 in a region syntenic to the murine locus Eae2. *Nature Genet* **13**: 477–480
Kuokkanen S, Gschwend M, Rioux JD *et al* 1997 Genomewide scan of multiple sclerosis in Finnish multiplex families. *Am J Hum Genet* **61**: 1379–1387
Kupersmith MJ, Alban T, Zeiffer B, Lefton D 2002 Contrast-enhanced MRI in acute optic neuritis: relationship to visual performance. *Brain* **125**: 812–822
Kupfer H, Monks CRF, Kupfer A 1994 Small splenic B cells that bind to antigen-specific T helper (Th) cells and face the site of cytokine production in the Th cells selectively proliferate: immunofluorescence microscopic studies of Th-B antigen-presenting cell interactions. *J Exp Med* **179**: 1507–1515
Kurdi A, Abdallat A, Ayesh I *et al* 1977 Different B lymphocyte alloantigens associated with multiple sclerosis in Arabs and Northern Europeans. *Lancet* **i**: 1123–1125
Kurenny DE, Moroz LL, Turner RW *et al* 1994 Modulation of ion channels in rod photoreceptors by nitric oxide. *Neuron* **13**: 315–324
Kurland LT 1952 The frequency and geographic distribution of multiple sclerosis as indicated by mortality stastistics and morbidity surveys in the United States and Canada. *Am J Hyg* **55**: 457–476
Kurland LT 1994 Trauma and multiple sclerosis. *Ann Neurol* **36 (Suppl)**: S33–S37
Kurland LT, Beebe GW, Kurtzke JF *et al* 1966 Studies on the natural history of multiple sclerosis. 2. The progression of optic neuritis to multiple sclerosis. *Acta Neurol Scand* **42 (Suppl 19)**: 157–176
Kurland LT, Molgaard CA, Kurland EM *et al* 1984 Swine flu vaccine and multiple sclerosis. *J Am Med Assoc* **251**: 2672–2675
Kuroiwa Y 1985 Concentric sclerosis. In: Koetsier JC (ed) *Handbook of Clinical Neurology*. Amsterdam: Elsevier, Vol 47, pp. 409–417
Kuroiwa Y, Igata A, Itahara K *et al* 1975 Nationwide survey of multiple sclerosis in Japan: clinical analysis of 1,084 cases. *Neurology* **25**: 845–51
Kuroiwa Y, Shibasaki S, Tabira T, Itoyama Y 1982 Clinical picture of multiple sclerosis in Asia. In: Kuroiwa Y, Kurland LT (eds) *Multiple Sclerosis East and West*. Kyushu: Kyushu University Press, pp. 31–47
Kuroiwa Y, Shibasaki H, Ikeda M 1983 Prevalence of multiple sclerosis and its north-south gradient in Japan. *Neuroepidemiology* **2**: 62–69
Kurtzke JF 1956 Course of exacerbations of multiple sclerosis hospitalised patients. *Arch Neurol Psychiatry* **76**: 175–184
Kurtzke JF 1961 On the evaluation of disability in multiple sclerosis. *Neurology* **11**: 686–694
Kurtzke JF 1965a Further notes on disability evaluation in multiple sclerosis, with scale modifications. *Neurology* **15**: 654–661
Kurtzke JF 1965b On the time of onset in multiple sclerosis. *Acta Neurol Scand* **41**: 140–158
Kurtzke JF 1967 Further considerations on the geographic distribution of multiple sclerosis. *Acta Neurol Scand* **43**: 283–297
Kurtzke JF 1970 Clinical manifestations of multiple sclerosis. In: Vinken PJ, Bruyn GW (eds) *Handbook of Clinical Neurology*. Amsterdam: Elsevier, Vol 9, pp. 161–216
Kurtzke JF 1974 Further features of the Fennoscandian focus of multiple sclerosis. *Acta Neurol Scand* **50**: 478–502
Kurtzke JF 1975 A reassessment of the distribution of multiple sclerosis. *Acta Neurol Scand* **51**: 110–157
Kurtzke JF 1977 Geography in multiple sclerosis. *J Neurol* **215**: 1–26
Kurtzke JF 1980a The geographic distribution of multiple sclerosis: an update with special reference to Europe and the Mediterranean region. *Acta Neurol Scand* **62**: 65–80
Kurtzke JF 1980b Epidemiologic contributions to multiple sclerosis – an overview. *Neurology* **30 (Part 2)**: 61–79
Kurtzke JF 1983a Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* **33**: 1444–1452
Kurtzke JF 1983b Epidemiology of multiple sclerosis. In: Hallpike JF, Adams CWM, Tourtellotte WW (eds) *Multiple Sclerosis: Pathology, Diagnosis and Management*. London: Chapman & Hall, pp. 47–95
Kurtzke JF 1985a Optic neuritis or multiple sclerosis. *Arch Neurol* 42: 704–710
Kurtzke JF 1985b Epidemiology of multiple sclerosis. In: Vinken PJ, Bruyn GW, Klawans HL (eds) *Handbook of Clinical Neurology*, revised series, *Demyelinating Diseases*. Amsterdam: Elsevier, Vol 3, pp. 259–287
Kurtzke JF 1988 Multiple sclerosis: what's in a name? *Neurology* **38**: 309–316
Kurtzke JF 1989 On estimating survival: a tale of two censors. *J Clin Epidemiol* **42**: 169–175
Kurtzke JF 1991 Multiple sclerosis: changing times. *Neuroepidemiology* **10**: 1–8
Kurtzke JF 1993 Epidemiologic evidence for multiple sclerosis as an infection. *Clin Microbiol Rev* **6**: 382–427

Kurtzke JF 1996 An introduction to neuroepidemiology. *Neuroepidemiology* **14**: 255–272
Kurtzke JF 2000 Epidemiology of multiple sclerosis: does this really point toward an etiology? Lectio Doctoralis. *Neurol Sci* **21**: 383–403
Kurtzke JF 2004 Origin of DSS: to present the plan. *Newsletter VA Special Interest Group Consortium MS Centers* **3**: 1–4
Kurtzke JF 2005 Epidemiology and etiology of multiple sclerosis. *Phys Med Rehab Clin N Am* **16**: 327–349
Kurtzke JF, Bui QH 1980 Multiple sclerosis in a migrant population: 2. Half Orientals immigrating in childhood. *Ann Neurol* 8: 256–260
Kurtzke JF, Heltberg A 2001 Multiple sclerosis in the Faroe Islands: an epitome. *J Clin Epidemiol* **54**: 1–22
Kurtzke JF, Hyllested K 1979 Multiple sclerosis in the Faroe islands: 1. Clinical and epidemiological features. *Ann Neurol* **5**: 6–21
Kurtzke JF, Hyllested K 1986 Multiple sclerosis in the Faroe Islands. II. Clinical update, transmission, and the nature of MS. *Neurology* **36**: 307–328
Kurtzke JF, Hyllested K 1987 Multiple sclerosis in the Faroe Islands. III. An alternative assessment of the three epidemics. *Acta Neurol Scand* **76**: 317
Kurtzke JF, Hyllested K 1988 Validity of the epidemics of multiple sclerosis in the Faroe islands. *Neuroepidemiology* **7**: 190–227
Kurtzke JF, Page 1997 Epidemiology of multiple sclerosis in US veterans. VII. Risk factors for MS. *Neurology* **48**: 204–213
Kurtzke JF, Beebe GW, Nagler B, Auth TL, Kurland LT, Nefzger MD 1968a Studies on natural history of multiple sclerosis. 4: Clinical features of the onset bout. *Acta Neurol Scand* **44**: 467–499
Kurzke JF, Park CS, Oh SJ 1968b Multiple sclerosis in Korea: clinical features and prevalence. *J Neurol Sci* **6**: 463–481
Kurtzke JF, Auth TL, Beebe GW *et al* 1969 Survival in multiple sclerosis. *Trans Am Neurol Assoc* **94**: 134–139
Kurtzke JF, Beebe GW, Nagler B, Nefzger MD, Auth TL, Kurland LT 1970a Studies on the natural history of multiple sclerosis 5: long-term survival in young men. *Arch Neurol* **22**: 215–225
Kurtzke JF, Dean G, Botha DPJ 1970b A method of estimating the age at immigration of white immigrants to South Africa with an example of its importance. *S Afr Med J* **44**: 663–669
Kurtzke JF, Kurland LT, Goldberg ID 1971 Mortality and migration in multiple sclerosis. *Neurology* **21**: 1186–1197
Kurtzke JF, Beebe GW, Nagler B *et al* 1973 Studies on the natural history of multiple sclerosis. 7: Correlates of clinical changes in an early bout. *Acta Neurol Scand* **49**: 379–395
Kurtzke JF, Beebe GW, Nagler B, Kurland LT, Auth TL 1977 Studies on the natural history of multiple sclerosis. 8. Early prognostic features of the later course of the illness. *J Chroni Dis* **30**: 819–830
Kurtzke, JF, Beebe GW, Norman Jr JE 1979 Epidemiology of multiple sclerosis in US veterans. 1. Race, sex, and geographic distribution. *Neurology* **29**: 1228–1235
Kurtzke JF, Gudmundsson KR, Bergmann S 1982 Multiple sclerosis in Iceland. 1. Evidence of a post-war epidemic. *Neurology* **32**: 143–150
Kurtzke JF, Beebe GW, Norman JE 1985 Epidemiology of multiple sclerosis in US veterans. III. Migration and the risk of MS. *Neurology* **35**: 672–678
Kurtzke JF, Hyllested K, Arbuckle JD *et al* 1988 Multiple sclerosis in the Faroe Islands. IV. The lack of a relationship between canine distemper and the epidemics of MS. *Acta Neurol Scand* **78**: 484–500
Kurtzke JF, Page WF, Murphy FM *et al* 1992 Epidemiology of multiple sclerosis in veterans. 4. Age at onset. *Neuroepidemiology* **11**: 226–235
Kurtzke JF, Hyllested K, Heltberg A, Olsen A 1993 Multiple sclerosis in the Faroe Islands. V. The occurrence of the fourth epidemic as validation of transmission. *Acta Neurol Scand* **88**: 161–173
Kurtzke JF, Hyllested K, Heltberg A 1995 Multiple sclerosis in the Faroe Islands: transmission across four epidemics. *Acta Neurol Scand* **91**: 321–325
Kurtzke JF, Hyllested K, Arbuckle JD *et al* 1997 Multiple sclerosis in the Faroe Islands. 7. Results of a case control questionnaire with multiple controls. *Acta Neurol Scand* **96**: 149–157
Kurtzke JF, Delasnerie-Laupretre N, Wallin MT 1998 Multiple sclerosis in North African migrants to France. *Acta Neurol Scand* **98**: 302–309
Kusuhara T, Nakajima M, Inoue H *et al* 2002 Parainfectious encephalomyeloradiculitis associated with herpes simplex virus 1 DNA in cerebrospinal fluid. *Clin Infect Dis* **34**: 1199–1205
Kuwabara S, Cappelen-Smith C, Lin CSY *et al* 2000 Excitability properties of median and peroneal motor axons. *Muscle Nerve* **23**: 1365–1373
Kuwabara S, Cappelen-Smith C, Lin CS *et al* 2001 Differences in accommodative properties of median and peroneal motor axons. *J Neurol Neurosurg Psychiatry* **70**: 372–376
Kutzelnigg A, Lucchinetti CF, Stadelmann C *et al* 2005 Cortical demyelination and diffiuse white matter injury in multiple sclerosis. *Brain* [epub ahead of print]
Kuwabara S, Ogawara K, Sung JY *et al* 2002 Differences in membrane properties of axonal and demyelinating Guillain-Barre syndromes. *Ann Neurol* **52**: 180–187
Kwon EE, Prineas JW 1994 Blood brain barrier abnormalities in longstanding multiple sclerosis lesions: an immunohistochemical study. *J Neuropathol Exp Neurol* **53**: 625–636
Kwon OJ, Karni A, Israel S *et al* 1999 HLA class II susceptibility to multiple sclerosis among Ashkenazi and non-Ashkenazi Jews. *Arch Neurol* **56**: 555–560
Laaksonen M, Pastinen T, Sjoroos M *et al* 2002 HLA class II associated risk and protection against multiple sclerosis – a Finnish family study. *J Neuroimmunol* **122**: 140–145
Laaksonen M, Jonasdottir A, Fossdal R *et al* 2003 A whole genome association study in Finish multiple sclerosis patients with 3669 markers. *J Neuroimmunol* **143**: 70–73
van der Laan LJW, Ruuls SR, Weber KS *et al* 1996 Macrophage phagocytosis of myelin *in vitro* determined by flow cytometry: phagocytosis is mediated by CR3 and induces production of tumor necrosis factor-α and nitric oxide. *J Neuroimmunol* **70**: 45–152
van der Laan LJ, van der Goes A, Wauben MH *et al* 2002 Beneficial effect of modified peptide inhibitor of alpha4 integrins on experimental allergic encephalomyelitis in Lewis rats. *J Neurosci Res* **67**: 191–199
Laan M, Wiebe V, Khusnutdinova E *et al* 2005 X-chromosome as a marker for population history: linkage disequilibrium and haplotype study in Eurasian populations. *Eur J Hum Genet* 13: 452–462
LaBan MM, Martin T, Pechur J, Sarnacki S 1998 Physical and occupational therapy in the treatment of patients with multiple sclerosis. *Phys Med Rehab Clin N Am* **9**: 603–614
Lacour A, De Seze J, Revenco E *et al* 2004 Acute aphasia in multiple sclerosis: a multicenter study of 22 patients. *Neurology* **62**: 974–977
Ladd H, Oist C, Jonnson B 1974 The effect of Dantrium® on spasticity in multiple sclerosis. *Acta Neurol Scand* **50**: 397–408
Ladiwala U, Lachance C, Simoneau SJ *et al* 1998 p75 neurotrophin receptor expression on adult human oligodendrocytes: signaling without cell death in response to NGF. *J Neurosci* **18**: 1297–1304
Ladiwala U, Li H, Antel JP, Nalbantoglu J 1999 Induction by tumor necrosis factor-alpha and involvement of p53 in cell death of human oligodendrocytes. *J Neurochem* **73**: 605–611
Lafaille JJ, Nagashima K, Katsuki M, Tonegawa S 1994 High incidence of spontaneous autoimmune encephalomyelitis in immunodeficient anti-myelin basic protein T cell receptor mice. *Cell* **78**: 399–408
Lafaille JJ, Keere FV, Hsu AL *et al* 1997 Myelin basic protein-specific T helper 2 (Th2) cells cause experimental autoimmune encephalomyelitis in immunodeficient hosts rather than protect them from disease. *J Exp Med* **186**: 307–312
Lagueny A, Arnaud A, Le Masson G *et al* 1998 Study of central and peripheral conductions to the diaphragm in 22 patients with definite multiple sclerosis. *Electromyogr Clin Neurophysiol* **38**: 333–342
Lai HM, Hodgson T, Gawne-Cain M *et al* 1996 A preliminary study into the sensitivity of disease activity detection by serial weekly magnetic resonance imaging in multiple

sclerosis. *J Neurol Neurosurg Psychiatry* **60**: 339–341
Lai K, Kaspar BK, Gage FH, Schaffer DV 2003 Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. *Nat Neurosci* **6**: 21–27
Lai MM, Kerrison JB, Miller NF 2004 Reversible bilateral internuclear ophthalmoplegia associated with FK506. *J Neurol Neurosurg Psychiatry* **75**: 776–778
Lakatos A, Smith PM, Barnett SC, Franklin RJ 2003 Meningeal cells enhance limited CNS remyelination by transplanted olfactory ensheathing cells. *Brain* **126**: 598–609
La Mantia L, Illeni MT, Milanese C *et al* 1990 HLA and multiple sclerosis in Italy: a review of the literature. *J Neurol* **237**: 441–444
La Mantia L, Eoli M, Milanese C, Salmaggi A, Dufour A, Torri V 1994 Double-blind trial of dexamethasone versus methylprednisolone in multiple sclerosis acute relapses. *Eur Neurol* **34**: 199–203
La Mantia L, Milanese C, Mascoli N *et al* 2002 Cyclophosphamide for multiple sclerosis. *Cochrane Database Syst Rev* **4**: CD002819
van Lambalgen R, Sanders EACM, D'Amaro J 1986 Sex distribution, age of onset and HLA profiles in two types of multiple sclerosis: a role for sex hormones and microbial infections in the development of autoimmunity. *J Neurol Sci* **76**: 13–21
Lambert S, Davis JQ, Bennett V 1997 Morphogenesis of the node of Ranvier: co-clusters of ankyrin and ankyrin-binding integral proteins define early developmental intermediates. *J Neurosci* **17**: 7025–7036
Lamers KH, van Engelen BG, Gabreels FJ, Hommes OR, Borm GF, Wevers RA 1995 Cerebrospinal neuron-specific enolase, S-100 and myelin basic protein in neurological disorders. *Acta Neurol Scand* **92**: 247–251
Lamers KJ, de-Reus HP, Jongen PJ 1998 Myelin basic protein in CSF as indicator of disease activity in multiple sclerosis. *Mult Scler* **4**: 124–126
Lammens M, Lissoir F, Carton H 1989 Hypothermia in three patients with multiple sclerosis. *Clin Neurol Neurosurg* **91**: 117–121
Lamoureux G, Duquette P, Lapiuerre Y *et al* 1983 HLA antigens-linked genetic control in multiple sclerosis patients resistant and susceptible to infection. *J Neurol* **230**: 91–104
Lampasona V, Franciotta D, Furlan R *et al* 2004 Similar low frequency of anti-MOG IgG and IgM in MS patients and healthy subjects. *Neurology* **62**: 2092–2094
Lampert PW, Carpenter S 1965 Electron microscopic studies on the vascular permeability and the mechanism of demyelination in experimental allergic encephalomyelitis. *J Neuropathol Exp Neurol* **24**: 11–24
Lana-Peixoto MA, Lana-Peixoto MI 1992 Is multiple sclerosis in Brazil and Asia alike? *Arq Neuropsiquiatr* **50**: 419–425
Lana-Peixoto MA, Teixeira A, The Brazilian Committee for Treatment and Research in Multiple Sclerosis (BCTRIMS) 2002 Simple phonic tic in multiple sclerosis. *Mult Scler* **8**: 510–511
Lander E, Krugylak L 1995 Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. *Nature Genet* **11**: 241–224
Landtblom AM, Riise T, Boiko A, Soderfeldt B 2002 Distribution of multiple sclerosis in Sweden based on mortality and disability compensation statistics. *Neuroepidemiology* **21**: 167–179
Landtblom AM, Wastenson M, Ahmadi A, Soderkvist P 2003 Multiple sclerosis and exposure to organic solvents, investigated by genetic polymorphisms of the GSTM1 and CYP2D6 enzyme systems. *Neurol Sci* **24**: 248–251
Landtblom AM, Riise T, Kurtzke JF 2005 Further considerations on the distribution of multiple sclerosis in Sweden. *Acta Neurol Scand* **111**: 238–246
Landy PJ 1983 A prospective study of the risk of developing multiple sclerosis in optic neuritis in a tropical and subtropical area. *J Neurol Neurosurg Psychiatry* **46**: 659–661
Lang HLE, Jacobsen H, Ikemizu S *et al* 2002 A functional and structural basis for TCR cross-reactivity in multiple sclerosis. *Nature Immunol* **3**: 940–943
Lange KFA 1913 Die Ausflockung kolloidalen Goldes dürch Zerebrospinalflüssigkeit bei luetischen Affektion des Zentralnervensystems. *Z Chemother* **1**: 44–78
Langer-Gould A, Atlas SW, Bollen AW, Pelletier D 2005 Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* **353**: 375–381
Langrish CL, Chen Y, Blumenschein WM *et al* 2005 IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med* **201**: 233–240
Lannes-Vieira J, Goudable B, Drexler K *et al* 1995 Encephalitogenic, myelin basic protein specific T cells from naive rat thymus: preferential use of the T cell receptor gene Vb8.2 and expression of the $CD4^{-}CD8^{-}$ phenotype. *Eur J Immunol* **25**: 611–616
Lapierre Y, Bouchard S, Tansey C, Gendron D, Barkas WJ, Francis GS 1987 Treatment of spasticity with tizanidine in multiple sclerosis. *Can J Neurol Sci* **14**: S13–S17
Lappe-Siefke C, Goebbels S, Gravel M *et al* 2003 Disruption of Cnp1 uncouples oligodendroglial functions in axonal support and myelination. *Nature Genet* **33**: 366–374
Largo C, Cuevas P, Somjen GG *et al* 1996 The effect of depressing glial function in rat brain *in situ* on ion homeostasis, synaptic transmission and neuron survival. *J Neurosci* **16**: 1219–1229
Larsen F, Oturai A, Ryder LP *et al* 2000 A linkage analysis of a candidate region in Scandinavian sib pairs with multiple sclerosis reveals linkage to chromosome 17q. *Genes Immun* **1**: 456–459
Larsen JP, Aarli JA, Riise T 1984 Western Norway, a high risk area for multiple sclerosis: a prevalence/incidence study in the county of Hordaland. *Neurology* **34**: 1202–1207
Larsson HBW, Frederiksen J, Kjaer L *et al* 1988 *In vivo* determination of T_1 and T_2 in the brain of patients with severe but stable multiple sclerosis. *Magn Reson Med* **7**: 43–55
Lassmann H 1983 Comparative neuropathology of chronic experimental allergic encephalomyelitis and multiple sclerosis. *Schrift Neurol* **25**: 1–135
Lassmann H 2003a Axonal injury in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **74**: 695–697
Lassmann H 2003b Brain damage when multiple sclerosis is diagnosed clinically. *Lancet* **361**: 1317–1318
Lassmann H, Vass K 1995 Are current immunological concepts of multiple sclerosis reflected by the immunopathology of its lesions? *Springer Semin Immunopathol* **17**: 77–87
Lassmann H, Wisniewski HM 1979a Chronic relapsing experimental allergic encephalomyelitis: clinicopathological comparison with multiple sclerosis. *Arch Neurol* **36**: 490–497
Lassmann H, Wisniewski HM 1979b Chronic relapsing experimental allergic encephalomyelitis: effect of age at the time of sensitization on clinical course and pathology. *Acta Neuropathol* **47**: 111–116
Lassmann H, Wisniewski HM 1979c Chronic relapsing experimental allergic encephalomyelitis: morphological sequence of myelin degradation. *Brain Res* **169**: 357–368
Lassmann H, Kitz K, Wisniewski HM 1980 Structural variability of demyelinating lesions in different models of subacute and chronic experimental allergic encephalomyelitis. *Acta Neuropathol* **51**: 191–201
Lassmann H, Budka H, Schnaberth G 1981a Inflammatory demyelinating polyradiculitis in a patient with multiple sclerosis. *Arch Neurol* **38**: 99–102
Lassmann H, Kitz K, Wisniewski HM 1981b *In vivo* effect of sera from animals with chronic relapsing experimental allergic encephalomyelitis on central and peripheral myelin. *Acta Neuropathol* **55**: 297–306
Lassmann H, Kitz K, Wisniewski HM 1981c The development of periventricular lesions in chronic relapsing experimental allergic encephalomyelitis in guinea pigs: a light and scanning electron microscope study. *Neuropathol Appl Neurobiol* **7**: 1–11
Lassmann H, Brunner C, Bradl M, Linington C 1988 Experimental allergic encephalomyelitis: the balance between encephalitogenic T lymphocytes and demyelinating antibodies determines size and structure of demyelinated lesions. *Acta Neuropathol* **75**: 566–576
Lassmann H, Zimprich F, Vass K, Hickey WF 1991a Microglial cells are a component of the perivascular glia limitans. *J Neurosci Res* **28**: 236–243

Lassmann H, Rössler K, Zimprich F, Vass K 1991b Expression of adhesion molecules and histocompatibility antigens at the blood-brain barrier. *Brain Pathol* **1**: 115–123

Lassmann H, Schmied M, Vass K, Hickey WF 1993 Bone marrow derived elements and resident microglia in brain inflammation. *Glia* **7**: 19–24

Lassmann H, Bartsch U, Montag D, Schachner M 1997 Dying back oligodendrogliopathy: a late sequel of myelin-associated glycoprotein deficiency. *Glia* **19**: 104–110

Lassmann H, Brück W, Lucchinetti C 2001 Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. *Trends Mol Med* **7**: 115–121

Lassmann H, Reindl M, Rauschka H *et al* 2003 A new paraclinical CSF marker for hypoxia-like tissue damage in multiple sclerosis lesions. *Brain* **126**: 1347–1357

Lataste X, Emre M, Davis C, Groves L 1994 Comparative profile of tizanidine in the management of spasticity. *Neurology* **44 (Suppl 9)**: S53–S59

Lauer K 1994 The risk of multiple sclerosis in the USA in relation to sociogeographic features: a factor-analytic study. *J Clin Epidemiol* **47**: 43–48

Lauer K, Firnhaber W 1987 Epidemiological investigations into multiple sclerosis in southern Hesse. V. Course and prognosis. *Acta Neurol Scand* **76**: 12–17

Lauer K, Firnhaber W 1994 Descriptive and analytical epidemiological data on multiple sclerosis from a long-term study in southern Hesse, Germany. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 147–158

Lauer K, Firnhaber W, Reining R, Leuchtweis B 1984 Epidemiological investigations into multiple sclerosis in Southern Hesse. I. Methodological problems and basic epidemiological characteristics. *Acta Neurol Scand* **70**: 257–265

Laughlin MJ, Barker J, Bambach B *et al* 2001 Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *N Engl J Med* **344**: 1815–1822

Laule C, Vavasour IM, Moore GR et al 2004 Water content and myelin water fraction in multiple sclerosis. A T2 relaxation study. *J Neurol* **251**: 284–293

Lavalle C, Pizarro S, Drenkard C, Sanchez-Guarro J, Alarcón-Segoria D 1990 Transverse myelitis: a manifestation of systemic lupus erythematosus strongly associated with antiphospholipid antibodies. *J Rheumatol* **17**: 34–37

Lawrence N, Oger J, Aziz T *et al* 2003 A sensitive radioimmunoprecipitation assay for assessing the clinical relevance of antibodies to IFN beta. *J Neurol Neurosurg Psychiatry* **74**: 1236–1239

Lawthom C, Durey P, Hughes T 2003 Constipation as a presenting symptom. *Lancet* **362**: 958

Laywell ED, Rakic P, Kukekov VG *et al* 2000 Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. *Proc Natl Acad Sci* **97**: 13883–13888

Lazarte JA 1950 Multiple sclerosis: prognosis for ambulatory and nonambulatory patients. *Assoc Res Nerv Ment Dis Proc* **28**: 512–523

Lazeron RH, Langdon DW, Filippi M *et al* 2000 Neuropsychological impairment in multiple sclerosis patients: the role of (juxta)cortical lesion on FLAIR. *Mult Scler* **6**: 280–285

Leandri M, Lundardi G, Inglese M *et al* 2000 Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis. *J Neurol* **247**: 556–558

Leao RN, Oikawa T, Rosa ES *et al* 2002 Isolation of dengue 2 virus from a patient with central nervous system involvement (transverse myelitis). *Rev Soc Bras Med Trop* **35**: 401–404

Leary SM, Davie CA, Parker GJ *et al* 1999 1H magnetic resonance spectroscopy of normal appearing white matter in primary progressive multiple sclerosis. *J Neurol* **246**: 1023–1026

Leary SM, McLean BN, Thompson EJ *et al* 2002 Local synthesis of IgA in the cerebrospinal fluid of patients with neurological diseases. *J Neurol* **247**: 609–615

Leary SM, Miller DH, Stevenson VL *et al* 2003 Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. *Neurology* **60**: 44–51

Leary SM, Porter B, Thompson AJ 2005 Multiple sclerosis: diagnosis and the management of acute relapses. *J Postgrad Med J* **81**:302–308

Lebar R, Lubetzki C, Vincent C *et al* 1986 The MS autoantigen of central nervous system myelin, a glycoprotein present in oligodendrocyte membranes. *Clin Exp Immunol* **66**: 423–434

Lee AG, Tang RA, Wong GG *et al* 2000 Isolated inferior rectus muscle palsy resulting from a nuclear third nerve lesion as the initial manifestation of multiple sclerosis. *J Neuroophthalmol* **20**: 246–247

Lee J, Elston J, Vickers S *et al* 1988 Botulinum toxin therapy for squint. *Eye* **2**: 24–28

Lee JC 1972 Evolution in the concept of the blood brain barrier phenomenon. In: Zimmermann HM (ed.) *Progress in Neuropathology*. New York: Grune & Stratton, pp. 84–145

Lee KH, Hashimoto SA, Hooge JP *et al* 1991 Magnetic resonance imaging of the head in the diagnosis of multiple sclerosis: a prospective 2-year follow-up with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology* **41**: 657–660

Lee MA, Smith S, Palace J *et al* 1999 Spatial mapping of T2 and gadolinium-enhancing T1 lesion volumes in multiple sclerosis: evidence for distinct mechanisms of lesion genesis? *Brain* **122**: 1261–1270

Lee MA, Reddy H, Johansen-Berg H *et al* 2000 The motor cortex shows adaptive functional changes to brain injury from multiple sclerosis. *Ann Neurol* **47**: 606–613

Lee MA, Blamire AM, Pendlebury S *et al* 2000 Axonal injury or loss in the internal capsule and motor impairment in multiple sclerosis. *Arch Neurol* **57**: 65–70

Lee SC, Raine CS 1989 Multiple sclerosis: oligodendrocytes in active lesions do not express class II major histocompatibility complex molecules. *J Neuroimmunol* **25**: 261–266

Lee SC, Moore GR, Golensky G, Raine CS 1990 Multiple sclerosis: a role for astroglia in active demyelination suggested by class II MHC expression and ultrastructural study. *J Neuropathol Exp Neurol* **49**: 122–136

Lee SC, Dickson DW, Brosnan CF 1995 Interleukin-1, nitric oxide and reactive astrocytes. *Brain Behav Immun* **9**: 345–354

Lee SJ, Benveniste EN 1999 Adhesion molecule expression and regulation on cells of the central nervous system. *J Neuroimmunol* 98: 77–88

Lee WB, Berger JR, O'Halloran HS 2003 Parinaud syndrome heralding MS. *Neurology* **60**: 322

Lees G 1998 Effects of pyrethroid molecules on rat nerves in vitro: potential to reverse temperature-sensitive conduction block of demyelinated peripheral axons. *Br J Pharmacol* **123**: 487–496

Legras A 1934 Multiple Sclerose bij Tweelingen. *Ned Tijdschr Geneeskd* **78**: 174–177

Le Hir M, Bluethmann H, Kosco-Vilbois MH *et al* 1996 Differentiation of follicular dendritic cells and full antibody responses require tumor necrosis factor receptor-1 signalling. *J Exp Med* **183**: 2367–2372

Lehman RAW, Fieger HG 1978 Arachnoid cyst producing recurrent neurological disturbances. *Surg Neurol* **10**: 134–136

Lehmann PV, Forsthuber T, Miller A, Sercarz EE 1992 Spreading of T-cell autoimmunity to cryptic determinants of an autoantigen. *Nature* **358**: 155–157

Lehmann PV, Sercarz EE, Forsthuber T *et al* 1993 Determinant spreading and the dynamics of the autoimmune T cell repertoire. *Immunol Today* **14**: 203–208

Lehnardt S, Lachance C, Patrizi S *et al* 2002 The toll-like receptor TLR4 is necessary for lipopolysaccharide-induced oligodendrocyte injury in the CNS. *J Neurosci* **22**: 2478–2486

Lehrmann E, Molinari A, Speciale C, Schwarcz R 2001 Immunohistochemical visualization of newly formed quinolinate in the normal and excitotoxically lesioned rat striatum. *Exp Brain Res* **141**: 389–397

Lehoczky T, Halasy-Lehoczky M 1963 Forme 'bénigne' de la sclérose en plaques. *La Presse Médicale* **71**: 2294–2296

LeHuen A, Lantz O, Beaudoin L *et al* 1998 Over-expression of natural killer T cells protects Va14-Ja281 transgenic nonobese mice against diabetes. *J Exp Med* **188**: 1831–1839

Leibowitz U, Alter M 1968 Optic nerve involvement as initial manifestation of multiple sclerosis. *Acta Neurol Scand* **44**: 70–80

Leibowitz U, Alter M 1970 Clinical factors associated with increased disability in multiple sclerosis. *Acta Neurol Scand* **46**: 53–70

Leibowitz U, Alter M 1973 *Multiple Sclerosis: Clues to its Cause*. Amsterdam: North Holland

Leibowitz U, Alter M, Halpern L 1964a Clinical studies of multiple sclerosis in Israel. III. Clinical course and prognosis related to age at onset. *Neurology* **14**: 926–932

Leibowitz U, Halpern L, Alter M 1964b Clinical studies of multiple sclerosis in Israel. I. A clinical analysis based on a country-wide survey. *Arch Neurol* **10**: 502–512

Leibowitz U, Antonovsky A, Kats R, Alter M 1967 Does pregnancy increase the risk of multiple sclerosis ? *J Neurol Neurosurg Psychiatry* **30**: 354–357

Leibowitz U, Kahana E, Alter M 1969 Survival and death in multiple sclerosis. *Brain* **92**: 115–130

Leibowitz U, Kahana E, Alter M 1970 Multiple sclerosis in immigrant and native populations of Israel. *Lancet* **i**: 1323–1325

Leibowitz U, Kahana E, Alter M 1972 Population studies of multiple sclerosis in Israel. In: Field EJ, Bell TM, Carnegie PRK (eds) *Multiple Sclerosis: Progress and Research*. Amsterdam: North Holland, pp. 179–196

Leidtke W, Edelmann W, Bieri PL *et al* 1996 GFAP is necessary for the integrity of CNS white matter architecture and long-term maintenance of myelination. *Neuron* **17**: 607–615

Leigh RJ, Zee DS 1999 *The Neurology of Eye Movements*, 3rd edn. New York: Oxford University Press

Leigh RJ, Burnstine TH, Ruff RL, Kasmer RJ 1991 The effect of anti-cholinergic agents upon acquired nystagmus: a double-blind study of trihexiphenidyl and trihexethyl chloride. *Neurology* **41**: 1737–1741

Lenman AJ, Tulley FM, Vrbova G *et al* 1989 Muscle fatigue in some neurological disorders. *Muscle Nerve* **12**: 938–942

Lennon VA, Wingerchuk DM, Kryzer TJ *et al* 2004 A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* **364**: 2106–2112

Lennon VA, Kryzer TJ, Pittock SJ *et al* 2005 IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med* **202**: 473–477

Lenschow DJ, Walunas TL, Bluestone JA 1996 CD28/B7 system of T cell costimulation. *Ann Rev Immunol* **14**: 233–258

Leocani L, Colombo B, Magnani G *et al* 2001 Fatigue in multiple sclerosis is associated with abnormal cortical activation to voluntary movement – EEG evidence. *Neuroimage* **13**: 1186–1192

Leonard JP, Waldburger KE, Goldman SJ 1995 Prevention of experimental autoimmune encephalomyelitis by antibodies against interleukin 12. *J Exp Med* **181:** 381–386

Lepore FE 1991 The origin of pain in optic neuritis. *Arch Neurol* **48**: 748–749

Lepore FE 1994 Uhthoff's symptom in disorders of the anterior visual pathways. *Neurology* **44**: 1036–1038

Leppert D, Waubant E, Burk M *et al* 1996 Interferon beta-1b inhibits gelatinase secretion and *in vitro* migration of human T cells: a possible mechanism for treatment efficacy in multiple sclerosis. *Ann Neurol* **40**: 846–852

Lesca G, Deschamps R, Lubetski C *et al* 2002 Acute myelitis in early *Borrelia burgdorferi* infection. *J Neurol* **249**: 1472–1474

Le Souef PN, Goldblatt J, Lynch NR 2000 Evolutionary adaptation of inflammatory immune responses in human beings. *Lancet* **356**: 242–244

Lester E, Feld E, Kinzie J, Wollmann R 1979 Necrotising myelopathy complicating Hodgkin's disease. *Arch Neurol* **36**: 583–585

Letournel F, Etcharry-Bouyx F, Verny C *et al* 2003 Two clinicopathological cases of a dominantly inherited, adult onset orthochromatic leucodystrophy. *J Neurol Neurosurg Psychiatry* **74**: 671–673

Leussink VI, Jung S, Merschdorf U *et al* 2001 High-dose methylprednisolone therapy in multiple sclerosis induces apoptosis in peripheral blood leukocytes. *Arch Neurol* **58**: 91–97

Leuzzi V, Lyon G, Cilio MR *et al* 1999 Childhood demyelinating diseases with a prolonged remitting course and their relation to Schilder's disease: report of two cases. *J Neurol Neurosurg Psychiatry* **66**: 407–408

Levesque M 1999 Interferon-beta 1 A-induced polyarthritis in a patient with the HLA-DRB1*0404 allele. *Arthritis Rheum* **42**: 569–573

Levin MC, Lee SM, Kalume F *et al* 2002 Autoimmunity due to molecular mimicry as a cause of neurological disease. *Nature Med* **8**: 509–513

Levine JM, Stincome F, Lee Y-S 1993 Development and differentiation of glial precursor cells in the rat cerebellum. *Glia* **7**: 307–321

Levine RA, Gardner JC, Fullerton BC *et al* 1994 Multiple sclerosis lesions of the auditory pons are not silent. *Brain* **117**: 1127–1141

Levine S, Hoenig EM 1968 Induced localization of allergic adrenalitis and encephalomyelitis at sites of thermal injury. *J Immunol* **100**: 1310–1318

Levine S, Sowinski R 1980 Experimental allergic encephalomyelitis: inhibition of clinical signs and paradoxical enhancement of lesions in second attacks. *Am J Pathol* **101**: 375–386

Levine S, Wenk EJ 1965 A hyperacute form of allergic encephalomyelitis. *Am J Path* **47**: 61–88

Levy-Bruhl D, Rebière I, Desenclos JC, Drucker J 1999 Comparaison entre les risques de premières atteintes démyélinisantes centrales aigües et les bénéfices de la vaccination contre l'hépatite B. *Bull Epidemiol hebdomadaire* **9**: 33–35

Lewis RA, Sumner AJ, Brown MJ, Asbury AK 1982 Multifocal demyelinating neuropathy with persistent conduction block. *Neurology* **32**: 958–964

Lexa FJ, Grossman RI 1994 MR of sarcoidosis of the head and spine: spectrum of manifestations and radiographic response to steroid therapy. *Am J Neuroradiol* **15**: 973–982

Leyden E 1863 Über graue Degeneration des Ruckenmarks. *Dtsch Klin* **15**: 121–128

Lhermitte F, Marteau R, Gazengel J *et al* 1973 The frequency of relapse in multiple sclerosis: a study based on 245 cases. *J Neurol* **205**: 47–59

Lhermitte F, Guillaumat L, Lyon-Caen O 1984 Monocular blindness with preserved direct and consensual pupillary reflex in multiple sclerosis. *Arch Neurol* **41**: 993–994

Lhermitte J, Bollak, Nicholas M 1924 Les douleurs à type de décharge électrique consécutives à la flexion céphalique dans la sclérose en plaques. *Rev Neurol* **42**: 56–62

Li DK, Paty DW 1999 Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing–remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis. *Ann Neurol* **46**: 197–206

Li DK, Zhao GJ, Paty DW, and The University of British Columbia MS MRI Analysis Research Group The Spectrims Study Group 2001 Randomized controlled trial of interferon-beta-1a in secondary progressive MS: MRI results. *Neurology* **56**: 1505–1513

Li H, Newcombe J, Groome NP, Cuzner ML 1993 Characterization and distribution of phagocytic macrophages in multiple sclerosis plaques. *Neuropathol Appl Neurobiol* **19**: 214–223

Li H, Jiang Y, Luning Prak E *et al* 2001 Editors and editing of anti-DNA receptors. *Immunity* **15**: 947–957

Li J, Hansen D, Mortensen PB, Olsen J 2002a Myocardial infarction in parents who lost a child: a nationwide prospective cohort study in Denmark. *Circulation* **106**: 1634–1639

Li J, Johansen C, Hansen D, Olsen J 2002b Cancer incidence in parents who lost a child: a nationwide study in Denmark. *Cancer* **95**: 2237–2242

Li J, Johnsen SP, Olsen J 2003a Stroke in parents who lost a child: a nationwide follow-up study in Denmark. *Neuroepidemiology* **22**: 211–216

Li J, Precht DH, Mortensen PB, Olsen J 2003b Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* **361**: 363–367

Li J, Johansen C, Bronnum-Hansen H *et al* 2004a The risk of multiple sclerosis in bereaved parents: a nationwide cohort study in Denmark. *Neurology* **62**: 726–729

Li J, Norgard B, Precht DH, Olsen J 2004b Psychological stress and inflammatory

bowel disease: a follow-up study in parents who lost a child in Denmark. *Am J Gastroenterol* **99**: 1129–1133
Li S, Stys PK 2001 Na(+)-K(+)-ATPase inhibition and depolarization induce glutamate release via reverse Na(+)-dependent transport in spinal cord white matter. *Neuroscience* **107**: 675–683
Li S, Mealing GA, Morley P, Stys PK 1999 Novel injury mechanism in anoxia and trauma of spinal cord white matter: glutamate release via reverse Na+-dependent glutamate transport. *J Neurosci* **19**: RC16
Li S, Jiang Q, Stys PK 2000 Important role of reverse Na+-Ca2+ exchange in spinal cord white matter injury at physiological temperature. *J Neurophysiol* **84**: 1116–1119
Li Y, Li H, Martin R, Mariuzza RA 2000 Structural basis for the binding of an immunodominant peptide from myelin basic protein in different registers by two HLA-DR2 proteins. *J Mol Biol* **304**: 177–188
Li Y, Li H, Dimasi N *et al* 2001 Crystal structure of a superantigen bound to the high-affinity, zinc-dependent site on MHC class II. *Immunity* **14**: 93–114
Li Z, Chapleau MW, Bates JN *et al* 1998 Nitric oxide as an autocrine regulator of sodium currents in baroreceptor neurons. *Neuron* **20**: 1039–1049
Liang L, Bickenbach JR 2002 Somatic epidermal stem cells can produce multiple cell lineages during development. *Stem Cells* **20**: 21–31
Liblau RS, van Endert P, Sandberg-Wollheim M *et al* 1993 Antigen processing gene polymorphisms in HLA-DR2 multiple sclerosis. *Neurology* **43**: 1192–1197
Liblau RS, Singer SM, McDevitt HO 1995 Th1 and Th2 $CD4^+$ T cells in the pathogenesis of organ-specific autoimmune diseases. *Immunol Today* **16**: 34–38
Lider O, Reshef T, Beraud E *et al* 1988 Anti-idiotypic network induced by T-cell vaccination against experimental autoimmune encephalomyelitis. *Science* **239**: 181–183
Lider O, Santos LMB, Lee CSY *et al* 1989 Suppression of experimental autoimmune encephalomyelitis by oral administration of myelin basic protein. II. Suppression of disease and *in vitro* immune responses is mediated by antigen specific $CD8^+$ T lymphocytes. *J Immunol* **142**: 748–752
Lieberman AP, Pitha PM, Shin HS, Shin ML 1989 Production of tumor necrosis factor and other cytokines by astrocytes stimulated with lipopolysaccharide or a neurotropic virus. *Proc Natl Acad Sci USA* **86**: 6348–6352
Liem KFJ, Jessell TM, Briscoe J 2000 Regulation of the neural patterning activity of sonic hedgehog by secreted BMP inhibitors expressed by notochord and somites. *Development* **127**: 4855–4866
Ligers A, Xu C, Saarinen S *et al* 1999 The CTLA-4 gene is associated with multiple sclerosis. *J Neuroimmunol* **97**: 182–190
Ligers A, Dyment DA, Willer CJ *et al* 2001a Evidence of linkage with HLA-DR in DRB1*1501-negative families with multiple sclerosis. *Am J Hum Genet* **69**: 900–903
Ligers A, Teleshova N, Masterman T *et al* 2001b CTLA-4 gene expression is influenced by promoter and exon-1 polymorphisms. *Genes Immun* **2**: 145–152
Lightman S, McDonald WI, Bird AC *et al* 1987 Retinal venous sheathing in optic neuritis: its significance for the pathogenesis of multiple sclerosis. *Brain* **110**: 405–414
Liguori M, Sawcer S, Setakis E *et al* 2003 A whole genome screen for linkage disequilibrium in multiple sclerosis performed in a continental italian population. *J Neuroimmunol* **143**: 97–100
Liguori M, Cittadella R, Manna I *et al* 2004 Association between synapsin III gene promoter polymorphisms and multiple sclerosis. *J Neurol* **251**: 165–170
Likosky WH, Fireman B, Elmore R *et al* 1991 Intense immunosuppression in chronic progressive multiple sclerosis: the Kaiser study. *J Neurol Neurosurg Psychiatry* **54**: 1055–1060
Lillien LE, Sendtner M, Raff MC 1990 Extracellular matrix-associated molecules collaborate with ciliary neurotrophic factor to induce type-2 astrocyte development. *J Cell Biol* **111**: 635–644
Lily O, Palace J, Vincent A 2004 Serum autoantibodies to cell surface determinants in multiple sclerosis: a flow cytometric study. *Brain* **127**: 269–279
Lim ET, Grant D, Pashenkov M *et al* 2004 Cerebrospinal fluid levels of brain specific proteins in optic neuritis. *Mult Scler* **10**: 261–265
Lim ET, Berger T, Reindl M *et al* 2005 Anti-myelin antibodies do not allow an earlier diagnosis of multiple sclerosis. *Mult Scler* **11**: 492–494
Lim KE, Hsu YY, Hsu WC, Chan CY 2003 Multiple complete ring-shaped enhanced MRI lesions in acute disseminated encephalomyelitis. *Clin Imaging* **27**: 281–284
Lima MASD, Bica RBS, Araujo AQC 2004 Gender influence on the progression of HTLV-I associated myelopathy/tropical spastic paraparesis. *J Neurol Neursurg Psychiatry* **76**: 294–296
Limburg CC 1950 The geographic distribution of multiple sclerosis and its estimated prevalence in the US. *Assoc Res Nerv Mental Dis* **28**: 15–24
Lin X, Turner B, Constantinescu CS *et al* 2002 Cerebral volume change in secondary progressive multiple sclerosis: effect of intravenous immunoglobulins (IVIG). *J Neurology* **249**: I169–I170
Lin X, Tench CR, Turner B *et al* 2003 Spinal cord atrophy and disability in multiple sclerosis over four years: application of a reproducible automated technique in monitoring disease progression in a cohort of the interferon β-1a (Rebif) treatment trial. *J Neurol Neurosurg Psychiatry* **74**: 1090–1094
Lincoln NB, Dent A, Harding J *et al* 2002 Evaluation of cognitive assessment and cognitive intervention for people with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **72**: 93–98
Lindå H, Hammarberg H, Cullheim S *et al* 1998 Expression of MHC class I and β2-microglobulin in rat spinal motoneurons: regulatory influences of IFN-gamma and axotomy. *Exp Neurol* **150**: 282–295
Lindberg C, Andersen O, Vahlne A *et al* 1991 Epidemiological investigation of the association between infectious mononucleosis and multiple sclerosis. *Neuroepidemiology* **10**: 62–65
Lindberg RLP, De Groot CJA, Montagne L *et al* 2001 The expression profile of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) in lesions and normal appearing white matter of multiple sclerosis. *Brain* **124**: 1743–1753
Linden D 1998a Autonomic evaluation by means of standard tests and power spectral analysis in multiple sclerosis. Reply. *Muscle Nerve* **20**: 679
Linden D 1998b Severe Raynaud's phenomenon associated with interferon-beta treatment for multiple sclerosis. *Lancet* **352**: 878–879
Linden D, Diehl RR, Kretzschmar A, Berlit P 1997 Autonomic evaluation by means of standard tests and power spectral analysis in multiple sclerosis. *Muscle Nerve* **20**: 809–814
Lindert R-B, Haase CG, Brehm U *et al* 1999 Multiple sclerosis: B- and T-cell responses to the extracellular domain of the myelin oligodendrocyte glycoprotein. *Brain* **122**: 2089–2099
Lindquist S, Schott BH, Ban M *et al* 2005 The BDNF-Val66Met polymorphism: implications for susceptibility to multiple sclerosis and severity of disease. *J Neuroimmunol* **67**: 183–185
Lindsberg PJ, Ohman J, Lehto T *et al* 1996 Complement activation in the central nervous system following blood-brain barrier damage in man. *Ann Neurol* **40**: 587–596
Lindsey JW 2005 Familial recurrence rates and genetic models of multiple sclerosis. *Am J Med Genet A* **135**: 53–58
Lindsey JW, Hodgkinson S, Mehta R *et al* 1994a Phase 1 clinical trial of chimeric monoclonal anti-CD4 antibody in multiple sclerosis. *Neurology* **44**: 413–419
Lindsey JW, Hodgkinson S, Mehta R *et al* 1994b Repeated treatment with chimeric anti-CD4 antibody in multiple sclerosis. *Ann Neurol* **36**: 183–189
Lindstedt M 1991 Multiple sclerosis – is research on the wrong track? *Med Hypotheses* **34**: 69–72
Linington C, Lassmann H 1987 Antibody responses in chronic relapsing experimental allergic encephalomyelitis: correlation of serum demyelinating activity with antibody titer to myelin/oligodendrocyte glycoprotein (MOG). *J Neuroimmunol* **17**: 61–70

Linington C, Webb M, Woodhams PL 1984 A novel myelin associated glycoprotein defined by a mouse monoclonal antibody. *J Neuroimmunol* **6**: 387–396

Linington C, Bradl M, Lassmann H *et al* 1988 Augmentation of demyelination in rat acute allergic encephalomyelitis by circulating mouse monoclonal antibodies directed against a myelin/oligodendrocyte glycoprotein. *Am J Pathol* **130**: 443–454

Linington C, Lassmann H, Morgan BP, Compston DAS 1989 Immunohistochemical localization of terminal complement component C9 in experimental allergic encephalomyelitis. *Acta Neuropathol* **79**: 78–85

Linington C, Engelhardt B, Kapocs G, Lassmann H 1992 Induction of persistently demyelinating lesions in the rat following the repeated adoptive transfer of encephalitogenic T cells and demyelinating antibodies. *J Neuroimmunol* **40**: 219–224

Link H 1967 Immunoglobulin G and low molecular weight proteins in human cerebrospinal fluid – chemical and immunological characterisation with special reference to multiple sclerosis. *Acta Neurol Scand* **43**: 1–136

Link H, Cruz M, Gessain A *et al* 1989 Chronic progressive myelopathy associated with HTLV-1: oligoclonal IgG and anti-HTLV-1 antibodies in cerebrospinal fluid and serum. *Neurology* **39**: 1566–1572

Link H, Baig S, Olsson O *et al* 1990 Persistent anti-myelin basic protein IgG antibody response in multiple sclerosis cerebrospinal fluid. *J Neuroimmunol* **28**: 237–248

Link J, Söderström M, Olsson T *et al* 1994 Increased transforming growth factor-α, interleukin-4 and interferon-γ in multiple sclerosis. *Ann Neurol* **36**: 379–386

Linker RA, Maurer M, Gaupp S *et al* 2002 CNTF is a major protective factor in demyelinating CNS disease: a neurotrophic cytokine as modulator in neuroinflammation. *Nature Med* **8**: 620–624

Linnebank M, Kesper K, Jeub M *et al* 2003 Hereditary elevation of angiotensin converting enzyme suggesting neurosarcoidosis. *Neurology* **61**: 1819–1820

Liour SS, Yu RK 2003 Differentiation of radial glia-like cells from embryonic stem cells. *Glia* **42**: 109–117

Lipton HL, Teasdell RD 1973 Acute transverse myelopathy in adults. *Arch Neurol* **28**: 252–257

Lipton MM, Freund J 1953 The transfer of experimental allergic encephalomyelitis in the rat by means of parabiosis. *J Immunol* **71**: 380–384

Lipton SA 1998 Neuronal injury associated with HIV-1: approaches and treatment. *Annu Rev Pharmacol Toxicol* **38**: 159–177

Lisak RP, Hirayama M, Kuchmy D *et al* 1983 Cultured human and rat oligodendrocytes and rat Schwann cells do not have immune response gene associated antigen (Ia) on their surface. *Brain Res* **289**: 285–292

Lisk D 1991 Multiple sclerosis in a west African. *Afr J Neurol Sci* **10**: 10–12

Litvan I, Grafman J, Vendell P *et al* 1988 Multiple memory defects in patients with multiple sclerosis. *Arch Neurol* **45**: 607–610

Litzenburger T, Fässler R, Bauer J *et al* 1998 B lymphocytes producing demyelinating autoantibodies: development and function in gene-targeted transgenic mice. *J Exp Med* **188**: 169–180

Litzenburger T, Blüthmann H, Morales P *et al* 2000 Development of MOG autoreactive transgenic B lymphocytes: receptor editing in vivo following encounter of a self-antigen distinct from MOG. *J Immunol* **165**: 5360–5366

Liu A, Stadelmann C, Moscarello M *et al* 2005 Expression of stathmin, a developmentally controlled cytoskeleton regulating molecule, in demyelinating disorders. *J Neurosci* **25**: 737–747

Liu C, Blumhardt LD 2000 Disability outcome measures in therapeutic trials of relapsing remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. *J Neurol Neurosurg Psychiatry* **68**: 450–457

Liu C, Playford ED, Thompson AJ 2003 Does neurorehabilitation have a role in relapsing–remitting multiple sclerosis? *J Neurol* **250**: 1214–1218

Liu H, Loo KK, Palaszynski K *et al* 2003 Estrogen receptor alpha mediates estrogen's immune protection in autoimmune disease. *J Immunol* **171**: 6936–6940

Liu J, Marino MW, Wong G *et al* 1998 TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination. *Nature Med* **4**: 78–83

Liu JS, Zhao ML, Brosnan CF, Lee SC 2001 Expression of inducible nitric oxide synthase and nitrotyrosine in multiple sclerosis lesions. *Am J Pathol* **158**: 2057–2066

Liu Q-S, Jia Y-S, Ju G 1997 Nitric oxide inhibits neuronal activity in the supraoptic nucleus of the rat hypothalamic slices. *Brain Res Bull* **43**: 121–125

Liu R, Cai J, Hu X *et al* 2003 Region-specific and stage-dependent regulation of Olig gene expression and oligodendrogenesis by Nkx6.1 homeodomain transcription factor. *Development* **130**: 6221–6231

Liu S, Qu Y, Stewart TJ *et al* 2000 Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation. *Proc Natl Acad Sci USA* **97**: 6126–6131

Liu Y, Rao MS 2004 Olig genes are expressed in a heterogeneous population of precursor cells in the developing spinal cord. *Glia* **45**: 67–74

Liu Z, Pelfrey CM, Cotleur A *et al* 2001 Immunomodulatory effects of interferon beta-1a in multiple sclerosis. *J Neuroimmunol* **112**: 153–162

Liuzzi GM, Trojano M, Fanelli M *et al* 2002 Intrathecal synthesis of matrix metalloproteinase-9 in patients with multiple sclerosis: implication for pathogenesis. *Mult Scler* **9**: 222–228

Llewellyn-Smith N, Lai M, Miller DH *et al* 1997 Effects of anti-CD4 antibody treatment on lymphocyte subsets and stimulated tumor necrosis factor alpha production: a study of 29 multiple sclerosis patients entered into a clinical trial of cM-T412. *Neurology* **48**: 810–816

Llorca J, Guerrero-Alonso P, Prieto-Salceda D 2005 Mortality trends of multiple sclerosis in Spain, 1951–1997: an age–period–cohort analysis. *Neuroepidemiology* **24**: 129–134

Lo AC, Black JA, Waxman SG 2002 Neuroprotection of axons with phenytoin in experimental allergic encephalomyelitis. *NeuroReport* **13**: 1909–1912

Lo AC, Saab CY, Black JA, Waxman SG 2003 Phenytoin protects spinal cord axons and preserves axonal conduction and neurological function in a model of neuroinflammation in vivo. *J Neurophysiol* **90**: 3566–3571

Lobnig BM, Chantelau E 2002 Multiple sclerosis and type 1 diabetes in Sardinia. *Lancet* **360**: 1253

Lock C, Hermans G, Pedotti R *et al* 2002 Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nature Med* **8**: 500–508

Lockwood CM, Thiru S, Isaacs JD *et al* 1993 Long-term remission of untreatable systemic vasculitis with monoclonal antibody therapy. *Lancet* **341**: 1620–1622

Lockyer MJ 1991 Prevalence of multiple sclerosis in five rural Suffolk practices. *Br Med J* **303**: 347–348

Loddenkemper T, Grote K, Evers S *et al* 2002 Neurological manifestations of the oculodentodigital dysplasia syndrome. *J Neurol* **249**: 584–595

Lodge PA, Allegretta M, Steinman L, Sriram S 1995 Myelin basic protein peptide specificity and T-cell receptor gene usage of HPRT mutant T-cell clones in patients with multiple sclerosis. *Ann Neurol* **36**: 734–740

Loers G, Aboul-Enein F, Bartsch U, Lassmann H 2004 Comparison of myelin, axon, lipid, and immunopathology in the central nervous system of differentially myelin-compromised mutant mice: a morphological and biochemical study. *Mol Cell Neurosci* **27**: 175–189

Loes DJ, Fatemi A, Melhem ER *et al* 2003 Analysis of MRI patterns aids prediction of progression in X-linked adrenoleucodystrophy. *Neurology* **61**: 369–374

Logan A, Frautschy SA, Gonzalez AM *et al* 1992 Enhanced expression of transforming growth factor beta1 in the rat brain after a localised cerebral injury. *Brain Res* **587**: 216–225

Logan A, Berry M, Gonzalez AM *et al* 1994 Effects of transforming growth factor beta1 on scar production in the injured central nervous system of the rat. *Eur J Neurosci* **6**: 355–363

Logigian EL, Kaplan RF, Steere AC 1990 Chronic neurologic manifestations of Lyme disease. *N Engl J Med* **323**: 1438–1444

Lopez Larrea C, Uria DF, Coto E 1990 HLA antigens in multiple sclerosis of northern Spanish population. *J Neurol Neurosurg Psychiatry* **53**: 434–435

Lord D, O'Farrell AGO, Staunton H, Keelan E 1990 The inheritance of MS susceptibility. *Irish J Med Sci* **159**: 1–20

Lord SE, Halligan PW, Wade DT 1998a Visual gait analysis: the development of a clinical assessment and scale. *Clinical Rehab* **12**: 107–119

Lord SE, Wade DT, Halligan PW 1998b A comparison of two physiotherapy treatment approaches to improve walking in multiple sclerosis: a pilot randomized controlled study. *Clinical Rehab* **12**: 477–486

Lorentzen JC, Issazadeh S, Storch M *et al* 1995 Protracted, relapsing and demyelinating experimental autoimmune encephalomyelitis in DA rats immunized with syngeneic spinal cord and incomplete Freund's adjuvant. *J Neuroimmunol* **63**: 193–205

Losseff NA, Wang L, Lai HM *et al* 1996a Progressive cerebral atrophy in multiple sclerosis: a serial MRI study. *Brain* **119**: 2009–2020

Losseff NA, Webb SL, O'Riordan JI *et al* 1996b Spinal cord atrophy and disability in multiple sclerosis: a new reproducible and sensitive MRI method with potential to monitor disease progression. *Brain* **119**: 701–708

Lossinsky AS, Badmajew V, Robson J, Moretz C, Wisniewski HM 1989 Sites of egress of inflammatory cells and horse radish peroxidase transport across the blood brain barrier in a murine model of chronic relapsing experimental allergic encephalomyelitis. *Acta Neuropathol* **78**: 359–371

Losy J, Niezgoda A 2001 IL-18 in patients with multiple sclerosis. *Acta Neurol Scand* **104**: 171–173

Lou J, Gasche Y, Zheng L *et al* 1999 Interferon-beta inhibits activated leukocyte migration through human brain microvascular endothelial cell monolayer. *Lab Invest* **79**: 1015–1025

Louis J-C, Magal E, Takayama S, Varon S 1993 CNTF protection of oligodendrocytes against natural and tumor necrosis factor-induced death. *Science* **259**: 689–692

Louis PCA 1825 *Recherches anatomico-pathologiques sur la phthisie*. Paris: Gabon

Lovas G, Szilagyi N, Majtenyi K *et al* 2000 Axonal changes in chronic demyelinated cervical spinal cord plaques. *Brain* **123**: 308–317

Love S, Gradidge T, Coakham HB 2001 Trigeminal neuralgia due to multiple sclerosis: ultrastructural findings in trigeminal rhizotomy specimens. *Neuropathol Appl Neurobiol* **27**: 238–244

Lovett-Racke AE, Martin R, McFarland HF *et al* 1997 Longitudinal study of myelin basic protein-specific T-cell receptors during the course of multiple sclerosis. *J Neuroimmunol* **78**: 162–171

Low NL, Carter S 1956 Multiple sclerosis in children. *Pediatrics* **18**: 24–39

Lowenthal A 1964 *Agar Gel Electrophoresis in Neurology*. Amsterdam: Elsevier

Lowenthal A, Van Sande M, Karcher D 1960 The differential diagnosis of neurological diseases by fractionating electrophoretically the CSF gamma globulins. *J Neurochem* **6**: 51–56

Lu F, Selak M, O'Connor J *et al* 2000 Oxidative damage to mitochondrial DNA and activity of mitochondrial enzymes in chronic active lesions of multiple sclerosis. *J Neurol Sci* **177**: 95–103

Lu JL, Sheikh KA, Wu HS *et al* 2000 Physiologic-pathologic correlation in Guillain-Barre syndrome in children. *Neurology* **54**: 33–39

Lu M, Zhang N, Maruyama M, Hawley RG, Ho AD 1996 Retrovirus-mediated gene expression in hematopoietic cells correlates inversely with growth factor stimulation. *Hum Gene Ther* **7**: 2263–2271

Lu QR, Yuk D, Alberta JA *et al* 2000 Sonic hedgehog-regulated oligodendrocyte lineage genes encoding bHLH proteins in the mammalian central nervous system. *Neuron* **25**: 317–329

Lu QR, Cai L, Rowitch D *et al* 2001 Ectopic expression of Olig1 promotes oligodendrocyte formation and reduces neuronal survival in developing mouse cortex. *Nat Neurosci* **4**: 973–974

Lu QR, Sun T, Zhu Z *et al* 2002 Common developmental requirement for Olig function indicates a motor neuron/oligodendrocyte connection. *Cell* **109**: 75–86

Lu W, Bhasin M, Tsirka SE 2002 Involvement of tissue plasminogen activator in onset and effector phases of experimental allergic encephalomyelitis. *J Neurosci* **22**: 10781–10789

Lublin FD, Reingold SC 1996 Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology* **46**: 907–911

Lublin FD, Whitaker JN, Eidelman BH, Miller AE, Arnason BGW, Burks JS 1996 Management of patients receiving interferon beta-1b for multiple sclerosis: report of a consensus conference. *Neurology* **46**: 12–18

Lublin FD, Reingold SC, the National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis 1997 Guidelines for clinical trials of new therapeutic agents in multiple sclerosis. *Neurology* **48**: 572–574

Lublin FD and the Hu 23F2G MS Study Group 1999 A Phase II trial of anti-cd11/cd18 monoclonal antibody in acute exacerbations of multiple sclerosis. *Neurology* **52**: A290

Lublin FD, Cutter G, Elfont R *et al* 2001 A trial to assess the safety of combining therapy with interferon beta-1a and glatiramer acetate in patients with relapsing MS. *Neurology* **56**: A148

Lublin FD, Baier M, Cutter G *et al* 2002 Results of the extension of a trial to assess the longer term safety of combining interferon beta-1a and glatiramer acetate. *Neurology* **58**: A85

Lublin FD, Baier M, Cutter G 2003 Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology* **61**: 1528–1532

Lucas J 1790 An account of uncommon symptoms succeeding the measles, with some additional remarks on the infection of measles and smallpox. *Lond Med J* **XI**: 325–331

Lucas M, Sanchez-Solino O, Solano F *et al* 1998 Interferon beta-1b inhibits reactive oxygen species production in peripheral blood monocytes of patients with relapsing–remitting multiple sclerosis. *Neurochem Int* **33**: 101–102

Lucchinetti CF, Brueck W, Rodriguez M, Lassmann H 1996 Distinct patterns of multiple sclerosis pathology indicates heterogeneity in pathogenesis. *Brain Pathol* **6**: 259–274

Lucchinetti CF, Kiers L, O'Duffy A *et al* 1997 Risk factors for developing multiple sclerosis after childhood optic neuritis. *Neurology* **49**: 1413–1418

Lucchinetti CF, Brück W, Parisi J *et al* 1999 A quantitative analysis of oligodendrocytes in multiple sclerosis lesions: a study of 117 cases. *Brain* **122**: 2279–2295

Lucchinetti CF, Brück W, Parisi J *et al* 2000 Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol* **47**: 707–717

Lucchinetti CF, Mandler R, McGavern D *et al* 2002 A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain* **125**: 1450–1461

Lucotte GL, Bathelier C, Mercier G 2000 TNF-alpha polymorphisms in multiple sclerosis: no association with –238 and –308 promoter alleles, but the microsatellite allele a11 is associated with the disease in French patients. *Mult Scler* **6**: 78–80

Lucotte GL, French MS Consortium 2002 Confirmation of a gene for multiple sclerosis (MS) to chromosome region 19q13.3. *Genet Couns* **13**: 133–138

Ludwin SK 1980 Chronic demyelination inhibits remyelination in the central nervous system: an analysis of contributing factors. *Lab Invest* **43**: 382–387

Ludwin SK 1990 Oligodendrocyte survival in Wallerian degeneration. *Acta Neuropathol* **80**: 184–191

Ludwin SK 1997 The pathobiology of the oligodendrocyte. *J Neuropathol Exp Neurol* **56**: 111–124

Ludwin SK, Johnson ES 1981 Evidence for a 'dying-back' gliopathy in demyelinating disease. *Ann Neurol* **9**: 301–305

Ludwin SK, Henry JM, McFarland H 2001 Vascular proliferation and angiogenesis in multiple sclerosis: clinical and pathogenetic

implications. *J Neuropathol Exp Neurol* **60**: 505
Lueck CJ, Pires M, Cartney ACE, Graham EM 1993 Ocular and neurological Behçet's disease without orogenital ulceration. *J Neurol Neurosurg Psychiatry* **56**: 505–508
Lugaresi A, Uncini A, Gambi D 1993 Basal ganglia involvement in multiple sclerosis with alternating side paroxysmal dystonia. *J Neurol* **240**: 257–261
Lujan S, Masjuan J, Roldan E *et al* 1998 The expression of integrins on activated T-cells in multiple sclerosis: effect of intravenous methylprednisolone treatment. *Mult Scler* **4**: 239–242
Lumsden CE 1970 The neuropathology of multiple sclerosis. In: Vinken PJ, Bruyn GW. *Handbook of Clinical Neurology*. Amsterdam: Elsevier, Vol 9, pp. 217–309
Lunardi G, Leandri M, Albano C *et al* 1997 Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. *Neurology* **48**: 1714–1717
Lundberg PO 1981 Sexual dysfunction in women with multiple sclerosis. *Int Rehab Med* **3**: 32–34
Lunding J, Midgard R, Vedeler CA 2002 Oligoclonal bands in cerebrospinal fluid: a comparative study of isoelectric focusing, agarose gel electrophoresis and IgG index. *Acta Neurol Scand* **102**: 322–325
Luo L, Salunga RC, Guo H *et al* 1999 Gene expression profiles of laser-captured adjacent neuronal cell types. *Nature Med* **1**: 122
Luomala M, Elovaara I, Koivula T, Lehtimaki T 1999 Intercellular adhesion molecule-1 K/E 469 polymorphism and multiple sclerosis. *Ann Neurol* **45**: 546–547
Luomala M, Elovaara I, Ukkonen M *et al* 2000 Plasminogen activator inhibitor 1 gene and the risk of MS in women. *Neurology* **54**: 1862–1864
Luomala M, Elovaara L, Ukkonen M *et al* 2001a The combination of HLA-DR1 and HLA-DR53 protects against MS. *Neurology* **56**: 383–385
Luomala M, Lehtimaka T, Elovaara I *et al* 2001b A study of interleukin-1 cluster genes in susceptibility to and severity of multiple sclerosis. *J Neurol Sci* **185**: 123–127
Luomala M, Lehtimaki T, Huhtala H *et al* 2003 Promoter polymorphism of IL-10 and severity of multiple sclerosis. *Acta Neurol Scand* **108**: 396–400
Lus G, Romano F, Scuotto A *et al* 2004 Azathioprine and interferon beta 1a in relapsing–remitting multiple sclerosis patients: increasing efficacy of combined treatment. *Eur Neurol* **51**: 15–20
Luster AD 1998 Chemokines – chemotactic cytokines that mediate inflammation. *N Engl J Med* **338**: 436–445
Luxton RW, Zeman A, Holzel H *et al* 1995 Affinity to antigen-specific IgG distinguishes multiple sclerosis from encephalitis. *J Neurol Sci* **132**: 11–19
Luys JB 1873 *Iconographie photographique des centres nerveux*. Paris: Baillière
Luyt K, Varadi A, Molnar E 2003 Functional metabotropic glutamate receptors are expressed in oligodendrocyte progenitor cells. *J Neurochem* **84**: 1452–1464
Lycke J, Wikkelso C, Bergh AC *et al* 1993 Regional cerebral blood flow in multiple sclerosis measured by single photon emission tomography with technetium-^{99m}hexamethylpropyleneamine oxime. *Eur Neurol* **33**: 163–167
Lycke J, Svennerholm B, Hjelmquist E *et al* 1996 Acyclovir treatment of relapsing–remitting multiple sclerosis: a randomised, placebo-controlled, double-blind study. *J Neurol* **243**: 214–224
Lycke JN, Karlsson J-E, Andersen O, Rosengren LE 1998 Neurofilament protein in cerebrospinal fluid: a potential marker of activity in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **64**: 402–404
Lycklama GT Nijeholt GJ, van Walderveen MA, Castelijns PA *et al* 1998 Brain and spinal cord abnormalities in multiple sclerosis: correlation between MRI parameters, clinical subtypes and symptoms. *Brain* **121**: 687–697
Lycklama GT, Thompson A, Filippi M *et al* 2003 Spinal-cord MRI in multiple sclerosis. *Lancet Neurol* **2**: 555–562
Lyman WD, Kadish AS, Raine CS 1981 Experimental allergic encephalomyelitis in the guinea pig: variation in peripheral blood lymphocyte responsiveness to myelin basic protein during disease development. *Cell Immunol* **63**: 409–416
Lynch JP 2003 Neurosarcoidosis: how good are the diagnostic tests? *J Neuroophthalmol* **23**: 187–189
Lynch SG, Rose JW, Smoker W, Petajan JH 1990 MRI in familial multiple sclerosis. *Neurology* **40**: 900–903
Lynch SG, Rose JW, Petagan JH *et al* 1991 Discordance of T-cell receptor beta-chain genes in familial multiple sclerosis. *Ann Neurol* **30**: 402–410
Lynch SG, Rose JW, Petagan JH, Leppert M 1992 Discordance of the T-cell receptor alpha-chain gene in familial multiple sclerosis. *Neurology* **42**: 839–844
Lynch SG, Peter K, LeVine SM 1996 Desferroxamine in chronic progressive multiple sclerosis: a pilot study. *Mult Scler* **2**: 157–160
Lynn B 1959 Retrobulbar neuritis: a survey of the present condition of cases occurring over the last fifty six years. *Trans Ophthalmol Soc UK* **50**: 262–267
Lyon-Caen O, Izquierdo G, Marteau R, Lhermitte F, Castaigne P, Hauw JJ 1985 Late onset multiple sclerosis: a clinical study of 16 pathologically proven cases. *Acta Neurol Scand* **72**: 56–60
Lyon-Caen O, Jouvert R, Hauser S *et al* 1986 Cognitive function in recent-onset demyelinating disease. *Arch Neurol* **43**: 1138–1141
Lyons J-A, San M, Happ MP, Cross AH 1999 B cells are critical to induction of experimental allergic encephalomyelitis by protein but not by a short encephalitogenic peptide. *Eur J Immunol* **29**: 3432–3439
Lyons PR, Newman PK, Saunders M 1988 Methylprednisolone therapy in multiple sclerosis: a profile of adverse effects. *J Neurol Neurosurg Psychiatry* **51**: 285–287
Ma JJ, Nishimura M, Mine H *et al* 1998 HLA-DRB1 and tumor necrosis factor gene polymorphisms in Japanese patients with multiple sclerosis. *J Neuroimmunol* **92**: 109–112
Ma RLZ, Gao JF, Meeker ND *et al* 2002 Identification of Bphs, an autoimmune disease locus, as histamine receptor H1. *Science* **297**: 620–623
MacAllister WS, Belman AL, Milazzo M *et al* 2005 Cognitive functioning in children and adolescents with multiple sclerosis. *Neurology* **64**: 1422–1425
McAlpine D 1931 Acute disseminated encephalomyelitis; its sequelae and relationship to disseminated sclerosis. *Lancet* **i**: 846–852
McAlpine D 1946 The problem of multiple sclerosis. *Brain* 69: 233–250
McAlpine D 1957 Familial incidence and role of hereditary factors in multiple sclerosis. 6th Congres international de neurologie: rapports et discussions. *Acta Med Belg* **(Suppl)**: 107–121
McAlpine D 1961 The benign form of multiple sclerosis: a study based on 241 cases seen within three years of onset and followed up until the tenth year or more of the disease. *Brain* **84**: 186–203
McAlpine D 1964 The benign form of multiple sclerosis: results of a long-term follow up. *Br Med J* **2**: 1029–1032
McAlpine D, Compston ND 1952 Some aspects of the natural history of disseminated sclerosis: incidence, course and prognosis: factors affecting onset and course. *Q J Med* **21**: 135–167
McAlpine D, Compston ND, Lumsden CE 1955 *Multiple Sclerosis*. Edinburgh: Livingstone
McAlpine D, Lumsden CE, Acheson ED 1965 *Multiple Sclerosis: a Re-appraisal*. Edinburgh: E. & S. Livingstone
McAlpine D, Lumsden CE, Acheson ED 1972 *Multiple Sclerosis: A Reappraisal*, 2nd edn. Edinburgh: Churchill Livingstone
McArthur JB 1987 Neurologic manifestations of AIDS. *Medicine* **66**: 407–437
McArthur JC, Young F 1986 Multiple sclerosis and pregnancy. In: Goldstein RJ (ed.) *Neurological Disorders of Pregnancy*. New York: Futura Publishing, pp. 197–211
McArthur JC, Haughey N, Gartner S *et al* 2003 Human immunodeficiency virus associated dementia: an evolving disease. *J Neurovirol* **9**: 205–221
McCall MG, Brereton T, Lee G *et al* 1968 Frequency of multiple sclerosis in 3 Australian cities – Perth, Newcastle and Hobart. *J Neurol Neurosurg Psychiatry* **31**: 1–9
McCarthy KD, De Vellis J 1980 Preparation of separate astroglial and oligodendroglial cell

cultures from rat cerebral tissue. *J Cell Biol* **85**: 890–902
McCombe PA, Nickson I, Tabi Z, Pender MP 1996 Corticosteroid treatment of experimental autoimmune encephalomyelitis in the Lewis rat results in the loss of Vβ8.2$^+$ and myelin basic protein-reactive cells from the spinal cord, with increased total T-cell apoptosis but reduced apoptosis of Vβ8.2$^+$ cells. *J Neuroimmunol* **70**: 93–101
McCoubrie M, Shuttleworth D 1978 The prevalence of multiple sclerosis in west Yorkshire. *Br Med J* **2**: 570
McDermott CJ, Grierson AJ, Wood JD *et al* 2003 Hereditary spastic paraparesis: disrupted intracellular transport associated with the spastin mutation. *Ann Neurol* **54**: 748–759
MacDonald BK, Cockerell OC, Sander JWAS, Shorvon SD 2000 The incidence and prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* **123**: 665–676
MacDonald JL, Roberts DF, Shaw DA, Saunders M 1976 Blood groups and other polymorphisms in multiple sclerosis. *J Med Genet* **13**: 30–33
McDonald JW, Liu X-Z, Qu Y *et al* 1999 Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. *Nature Med* **5**: 1410–1412
MacDonald SC, Simcoff R, Jordan LM *et al* 2002 A population of oligodendrocytes derived from multipotent neural precursor cells expresses a cholinergic phenotype in culture and responds to ciliary neurotrophic factor. *J Neurosci Res* **68**: 255–264
McDonald WI 1961 Conduction velocity of cutaneous afferent fibres during experimental demyelination. *Proc University Otago Med Schl* **39**: 29–30
McDonald WI 1962 Conduction in muscle afferent fibres during experimental demyelination in cat nerve. *Acta Neuropathol* **l**: 425–432
McDonald WI 1963 The effects of experimental demyelination on conduction in peripheral nerve: a histological and electrophysiological study. II. Electrophysiological observations. *Brain* **86**: 501–524
McDonald WI 1975 Mechanisms of functional loss and recovery in spinal cord damage. In: *Outcome of Severe Damage to the Central Nervous System, Ciba Foundation Symposium*. pp. 23–33
McDonald WI 1982 Clinical consequences of conduction defects produced by demyelination. In: Culp WJ, Ochoa J (eds) *Abnormal Nerves and Muscles as Impulse Generators*. Oxford: Oxford University Press, pp. 253–270
McDonald WI 1983 Attitudes to the treatment of multiple sclerosis. *Arch Neurol* **40**: 667–670
McDonald WI 1986 The pathophysiology of multiple sclerosis. In: McDonald WI, Silberberg DH (eds) *Multiple Sclerosis*. London: Butterworths, pp. 112–133
McDonald WI 1994 The pathological and clinical dynamics of multiple sclerosis. *J Neuropathol Exp Neurol* **53**: 338–343
McDonald WI 1998 Pathophysiology of multiple sclerosis. In: Compston A, Ebers G, Lassmann H *et al* (eds) *McAlpine's Multiple Sclerosis*, 3rd edn. London: Churchill Livingstone, pp. 359–378
McDonald WI 2002 Multiple sclerosis in its European matrix. *Mult Scler* **8**: 181–191
McDonald WI 2004 Multiple sclerosis in its European matrix: some aspects of history, mechanisms and treatment. *Can J Neurol Sci* **31**: 37–47
McDonald WI, Barnes D 1989 Lessons from magnetic resonance imaging in multiple sclerosis. *Trends Neurosci* **12**: 376–379
McDonald WI, Barnes D 1992 The ocular manifestations of multiple sclerosis. 1 Abnormalities of the afferent visual system. *J Neurol Neurosurg Psychiatry* **55**: 747–752
McDonald WI, Halliday AM 1977 Diagnosis and classification of multiple sclerosis. *Br Med Bull* **33**: 4–9
McDonald WI, Sears TA 1969 Effect of demyelination on conduction in the central nervous system. *Nature* **221**: 182–183
McDonald WI, Sears TA 1970 The effects of experimental demyelination on conduction in the central nervous system. *Brain* **93**: 583–598
McDonald WI, Silberberg DH 1986 The diagnosis of multiple sclerosis. In: McDonald WI, Silberberg DH (eds) *Multiple Sclerosis*. London: Butterworths, pp. 1–10
McDonald WI, Miller DH, Thompson AJ 1994 Are magnetic resonance findings predictive of clinical outcome in therapeutic trials in multiple sclerosis? The dilemma of interferon-β. *Ann Neurol* **36**: 14–18
McDonald WI, Compston A, Edan G *et al* 2001 Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* **50**: 121–127
McDonnell GV, Hawkins SA 1996 Primary progressive multiple sclerosis: a distinct syndrome? *Mult Scler* **2**: 137–141
McDonnell GV, Hawkins SA 1998a An epidemiological study of multiple sclerosis in Northern Ireland. *Neurology* **50**: 423–428
McDonnell GV, Hawkins SA 1998b Clinical study of primary progressive multiple sclerosis in Northern Ireland, UK. *J Neurol Neurosurg Psychiatry* **64**: 451–454
McDonnell GV, Hawkins SA 1999 High incidence and prevalence of multiple sclerosis in south-east Scotland: evidence of a genetic predisposition (letter). *J Neurol Neursurg Psychiatry* **66**: 411
McDonnell GV, Hawkins SA 2000 Multiple sclerosis in northern Ireland: a historical and global perspective. *Ulster Med J* **69**: 97–105
McDonnell GV, Hawkins SA 2002 Primary progressive multiple sclerosis: increasing clarity but many unanswered questions. *J Neurol Sci* **199**: 1–15
McDonnell GV, Kirk CW, Middleton D *et al* 1999a Genetic association studies of tumour necrosis factor α and β and tumour necrosis factor receptor 1 and 2 polymorphisms across the clinical spectrum of multiple sclerosis. *J Neurol* **246**: 1051–1058
McDonnell GV, Mawhinney H, Graham CA *et al* 1999b A study of the HLA-DR region in clinical subgroups of multiple sclerosis and its influence on prognosis. *J Neurol Sci* **165**: 77–83
McDonnell GV, Kirk CW, Hawkins SA, Graham CA 1999c Lack of association of transforming growth factor (TGF)beta1 and beta2 gene polymorphisms with multiple sclerosis (MS) in northern Ireland. *Mult Scler* **5**: 105–109
McDonnell GV, Kirk CW, Hawkins SA, Graham CA 2000 An evaluation of interleukin genes as susceptibility loci for multiple sclerosis. *J Neurol Sci* **176**: 4–12
McDonnell GV, Cabrera-Gomez J, Calne DB *et al* 2003 Clinical presentation of primary progressive multiple sclerosis 10 years after the incidental finding of typical magnetic resonance imaging brain lesions: the subclinical stage of primary progressive multiple sclerosis may last 10 years. *Mult Scler* **9**: 210–212
McDonough J, Dutta R, Gudz T *et al* 2003 Decreases in GABA and mitochondrial genes are implicated in MS cortical pathology through microarray analysis of postmortem MS cortex. *Soc Neurosci Abstr* **213**: 212
McDougall AJ, McLeod JG 2003 Autonomic nervous system function in multiple sclerosis. *J Neurol Sci* **215**: 79–85
McFarland HF 1992 Twin studies and multiple sclerosis. *Ann Neurol* **32**: 722–723
McFarland HF, Frank J, Albert P *et al* 1992 Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. *Ann Neurol* **32**: 758–766
McFarling DA, Susac JO 1979 Hoquet diabolique: intractable hiccups as a manifestation of multiple sclerosis. *Neurology* **26**: 797–801
McGavern DB, Murray PD, Rivera-Quinones C *et al* 2000 Axonal loss results in spinal cord atrophy, electrophysiological abnormalities and neurological deficits following demyelination in a chronic inflammatory model of multiple sclerosis. *Brain* **123**: 519–531
McGeer PL, Itagaki S, Boyes BE, McGeer EG 1988 Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology* **38**: 1285–1291
McGeoch DJ 2001 Molecular evolution of the γ-Herpesvirinae. *Phil Trans R Soc Lond* **356**: 421–435
MacGregor HS 1991 Multiple sclerosis clusters in Florida. *J Epidemiol Commun Hlth* **45**: 88
McGrother CW, Dugmore C, Phillips MJ *et al* 1999 Multiple sclerosis, dental caries and

fillings: a case-control study. *Brit Dent J* **187**: 261–264
McGuigan C, McCarthy A, Quigley C *et al* 2004 Latitudinal variation in the prevalence of multiple sclerosis in Ireland, an effect of genetic diversity. *J Neurol Neurosurg Psychiatry* **75**: 572–576
McHenry L 1969 *Garrison's History of Neurology*. Springfield, IL: C.C. Thomas, pp. 253–254
McHugh K, McMenamin JB 1987 Acute disseminated encephalomyelitis in childhood. *Irish Med J* **80**: 412–414
McIntosh-Michaelis SA, Roberts MH, Wilkinson SM *et al* 1991 The prevalence of cognitive impairment in a community survey of multiple sclerosis. *Br J Clin Psychol* **30**: 333–348
McIvor GP, Riklan M, Reznikoff M 1984 Depression in multiple sclerosis as a function of length and severity of illness, age, remissions and perceived social support. *J Neuropsychol* **40**: 1028–1033
MacKarell P 1990 *Depictions of an Odyssey*. Corsham, Wiltshire: National Society for Education in Art and Design
MacKay A, Whittall K, Adler J *et al* 1994 In vivo visualization of myelin water in brain by magnetic resonance. *Magn Reson Med* **31**: 673–677
MacKay JR, Goldstein G 1967 Thymus and muscle (letter to editor). *Clin Exp Immunol* **2**: 139–140
McKay RD 1999 Brain stem cells change their identity. *Nature Med* **5**: 261–262
Mackay RP 1950 The familial recurrence of multiple sclerosis. In: *Multiple Sclerosis and the Demyelinating Diseases*. *Proc Assoc Res Nerv Mental Dis* **28**: 150–177
Mackay RP 1953 Multiple sclerosis: its onset and duration. *Med Clin N Am* **37**: 511–521
Mackay RP, Hirano A 1967 Forms of benign multiple sclerosis: report of two 'clinically silent' cases discovered at autopsy. *Arch Neurol* **17**: 588–600
Mackay RP, Myrianthopoulous NC 1958 Multiple sclerosis in twins: preliminary report in twins and their relatives. *Arch Neurol Psychiatry* **80**: 667–674
Mackay RP, Myrianthopoulous NC 1966 Multiple sclerosis in twins and their relatives: final report. *Arch Neurol* **15**: 449–462
MacKenzie W 1840 *A Practical Treatise on Diseases of the Eye*, 3rd edn. London: Longman
MacKenzie-Graham A, Pribyl TM, Kim S *et al* 1997 Myelin protein expression is increased in lymph nodes of mice with relapsing experimental autoimmune encephalomyelitis. *J Immunol* **159**: 4602–4610
McKeown LP, Porter-Armstrong AP, Baxter GD 2004 Caregivers of people with multiple sclerosis: experiences of support. *Mult Scler* **10**: 219–230
McKeown SR, Allen IV 1978 The cellular origin of lysosomal enzymes in the plaque of multiple sclerosis: a combined histological and biochemical study. *Neuropath Appl Neurobiol* **4**: 471–482
McKerracher L, David S, Jackson DL *et al* 1994 Identification of myelin associated glycoprotein as a major myelin-derived inhibitor of neurite growth. *Neuron* **13**: 805–811
McKinnon PJ, Margolskee RF 1996 SC1: a marker for astrocytes in the adult rodent brain is upregulated during reactive astrocytosis. *Brain Res* **709**: 27–36
McKinnon RD, Dubois-Dalcq M 1990 Fibroblast growth factor blocks myelin basic protein gene expression in differentiating O-2A glial progenitor cells. *Ann NY Acad Sci* **605**: 358–359
McKinnon RD, Piras G, Ida JA, Dubois-Dalcq M 1993 A role for TGF-beta in oligodendrocyte differentiation. *J Cell Biol* **121**: 1397–1407
McKinnon RD, Waldron S, Kiel ME 2005 PDGF alpha-receptor signal strength controls an RTK rheostat that integrates phosphoinositol 3′-kinase and phospholipase gamma pathways during oligodendrocyte maturation. *J Neurosci* **25**: 3499–3508
McLarnon JG, Michikawa M, Kim SU 1993 Effects of tumor necrosis factor on inward potassium current and cell morphology in cultured human oligodendrocytes. *Glia* **9**: 120–126
MacLaurin H 1873 Case of amblyopia from partial neuritis, treated with subcutaneous injections of strychnia. *NSW Med Gazette* **3**: 214
McLean AR, Berkson J 1951 Mortality and disability in multiple sclerosis: a statistical estimate of prognosis. *J Am Med Assoc* **146**: 1367–1369
MacLean AR, Berkson J, Woltmnan HW, Schionneman L 1950 Multiple sclerosis in a rural community. *Arch Res Nerv Mental Dis Proc* **28**: 25–27
McLean BN, Luxton RW, Thompson EJ 1990 A study of immunoglobulin G in the cerebrospinal fluid of 1007 patients with suspected neurological disease using isoelectric focusing and the log IgG-index: a comparison and diagnostic applications. *Brain* **113**: 1269–1289
McLean BN, Zeman AZ, Barnes D, Thompson EJ 1993 Patterns of blood brain barrier impairment and clinical features in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **56**: 356–360
MacLennan ICM 1994 Germinal centers. *Annu Rev Immunol* **12**: 117–139
McLeod J, Hammond SR, Hallpike JF 1994 Epidemiology of multiple sclerosis in Australia. *Med J Aust* **160**: 117–119, 121–122
McLuckie A, Savage R 1993 Atrial fibrillation following methylprednisolone pulse therapy in an adult. *Chest* **104**: 622–623
Maclure M 1991 The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 133: 144–153
McMahon BJ, Helminiak C, Wainwright RB *et al* 1992 Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* **92**: 254–256
McMahon JA, Takada S, Zimmerman LB *et al* 1998 Noggin-mediated antagonism of BMP signaling is required for growth and patterning of the neural tube and somite. *Genes Dev* **12**: 1438–1452
McManus C, Berman JW, Brett FM *et al* 1998 MCP-1, MCP-2 and MCP-3 expression in multiple sclerosis lesions: an immunohistochemical and in situ hybridization study. *J Neuroimmunol* **86**: 20–29
McMenamin PG 1999 Distribution and phenotype of dendritic cells and resident tissue macrophages in the dura mater, leptomeninges, and choroid plexus of the rat brain as demonstrated in wholemount preparations. *J Comp Neurol* **405**: 553–562
McNatt SA, Yu C, Giannotta SL *et al* 2005 Gamma knife radiosurgery for trigeminal neuralgia. *Neurosurgery* **56**: 1295–301; discussion 1301–1303
McPherson D, Starr A 1993 Auditory evoked potentials in the clinic. In: Halliday AM (ed.) *Evoked Potentials in Clinical Testing*. Edinburgh: Churchill Livingstone, pp. 359–381
McQualter JL, Darwiche R, Ewing C *et al* 2001 Granulocyte macrophage colony-stimulating factor: a new putative therapeutic target in multiple sclerosis. *J Exp Med* **194**: 873–882
McRae BL, Semnani RT, Hayes MP, van Seventer GA 1998 Type I IFNs inhibit human dendritic cell IL-12 production and Th1 cell development. *J Immunol* **160**: 4298–4304
McTigue DM, Horner PJ, Stokes BT, Gage FH 1998 Neurotrophin-3 and brain-derived neurotrophic factor induce oligodendrocyte proliferation and myelination of regenerating axons in the contused adult rat spinal cord. *J Neurosci* **18**: 5354–5365
Madigand DM, Oger JJ-F, Fauchet R *et al* 1982 HLA profiles in multiple sclerosis suggest two forms of disease and the existence of protective haplotypes. *J Neurol Sci* **53**: 519–529
Madsen LS, Andersson EC, Jansson L *et al* 1999 A humanized model for multiple sclerosis using HLA DR2 and a human T cell receptor. *Nature Genet* **23**: 343–347
Maeda A, Sobel RA 1996 Matrix metalloproteinases in the normal human central nervous system, microglia nodules and multiple sclerosis lesions. *J Neuropathol Exp Neurol* **55**: 300–309
Maeda Y, Solansky M, Menonna J *et al* 2001 Platelet-derived growth factor-alpha receptor-positive oligodendroglia are frequent in multiple sclerosis lesions. *Ann Neurol* **49**: 776–785
Maehlen J, Olsson T, Zachau A, Klareskog L 1989 Local enhancement of major histocompatibility complex (MHC) class I and class II expression and cell infiltration in experimental allergic encephalomyelitis around axotomized motor neurons. *J Neuroimmunol* **23**: 125–132

Maglivi SS, Leavitt BR, Macklis JD 2000 Induction of neurogenesis in the neocortex of adult mice. *Nature* **405**: 951–955

Magnus T, Chan A, Grauer O *et al* 2001 Microglial phagocytosis of apoptotic inflammatory T cells leads to down-regulation of microglial immune activation. *J Immunol* **167**: 5004–5010

Magnus T, Chan A, Linker RA *et al* 2002 Astrocytes are less efficient in the removal of apoptotic lymphocytes than microglia cells: implications for the role of glial cells in the inflamed central nervous system. *J Neuropathol Exp Neurol* **61**: 760–766

Magy L, Mertens C, Avellana-Adalid V *et al* 2003 Inducible expression of FGF2 by a rat oligodendrocyte precursor cell line promotes CNS myelination in vitro. *Exp Neurol* **184**: 912–922

Mahad DJ, Howell SJ, Woodroofe MN 2002 Expression of chemokines in the CSF and correlation with clinical disease activity in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **72**: 498–502

Mahad DJ, Trebst C, Kivisäkk P *et al* 2004 Expression of chemokine receptors CCR1 and CCR5 reflects differential activation of mononuclear phagocytes in pattern II and pattern III multiple sclerosis lesions. *J Neuropath Exp Neurol* **63**: 262–273

Mahassin F, Algayres JP, Valmary J *et al* 1993 Myélite aigüe après vaccination contre l'hépatite B. *Presse Med* **22**: 1997–1998

Maier K, Rau CR, Storch MK *et al* 2004 Ciliary neurotrophic factor protects retinal ganglion cells from secondary cell death during acute autoimmune optic neuritis in rats. *Brain Pathol* **14**: 378–387

Maimone D, Reder AT, Finocchiaro F, Recupero E 1991a Internal capsule plaque and tonic spasms in multiple sclerosis. *Arch Neurol* **48**: 427–429

Maimone D, Gregor S, Arnason BG, Reder AT 1991b Cytokine levels in the cerebrospinal fluid and serum of patients with multiple sclerosis. *J Neuroimmunol* **32**: 67–74

Mainero C, Faroni J, Gasperini C *et al* 1999 Fatigue and magnetic resonance imaging activity in multiple sclerosis. *J Neurol* **246**: 454–458

Majed H, Chandran SC, Niclou S *et al* 2005 A novel role for Sema3A in neuroprotection from injury mediated by activated microglia. (submitted)

Majid A, Galetta SL, Sweeney CJ *et al* 2002 Epstein–Barr virus myeloradiculitis and encephalomyeloradiculitis. *Brain* **125**: 159–165

Malcus-Vocanson C, Giraud P, Broussolle E, Perron H, Mandrand B, Chazot G 1998 A urinary marker for multiple sclerosis. *Lancet* **351**: 1330

Malcus-Vocanson C, Giraud P, Micoud F *et al* 2001 Glial toxicity in urine and multiple sclerosis. *Mult Scler* **7**: 383–388

Male DK, Pryce G, Hughes CCW 1987 Antigen presentation in brain: MHC induction on brain endothelium and astrocyte compared. *Immunology* **60**: 453–459

Male DK, Pryce G, Rahman J 1990 Comparison of the immunological properties of rat cerebral and aortic endothelium. *J Neuroimmunol* **30**: 161–168

Male DK, Rahman J, Pryce G *et al* 1994 Lymphocyte migration into the CNS modelled in vitro: roles of LFA-1, ICAM-1 and VLA-4. *Immunology* **81**: 366–372

Malferrari G, Stella A, Monferini E *et al* 2005 CTLA4 and multiple sclerosis in the Italian population. *Exp Mol Pathol* **78**: 55–57

Malhotra AS, Goren H 1981 The hot bath test in the diagnosis of multiple sclerosis. *J Am Med Assoc* **246**: 1113–1114

Malik O, Compston DAS, Scolding NJ 1998 Interferon-beta inhibits astrocyte proliferation *in vitro*. *J Neuroimmunol* 1998 **86**: 155–162

Malipiero U, Frei K, Spanaus K-S *et al* 1997 Myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis is chronic/relapsing in perforin knockout mice, but monophasic in Fas- and Fas ligand-deficient lpr and gld mice. *Eur J Immunol* **27**: 3151–3160

Malmgren RM, Valdiviezo NL, Visscher BR *et al* 1983 Underlying cause of death as recorded for multiple sclerosis patients: associated factors. *J Chronic Dis* **36**: 699–705

Malone PR, Stanton SL, Riddle PR 1985 Urinary diversion for incontinence – a beneficial procedure? *Ann R Coll Surg Engl* **76**: 349–352

Malucchi S, Sala A, Gilli F *et al* 2004 Neutralizing antibodies reduce the efficacy of IFN during treatment of multiple sclerosis. *Neurology* **62**: 2031–2037

Manabe Y, Sasaki C, Warita H *et al* 2000 Sjogren's syndrome with acute transverse myelopathy as the initial manifestation. *J Neurol Sci* **176**: 158–161

Management of Multiple Sclerosis in Primary and Secondary Care. Clinical Guideline 8, November 2003. www.nice.org.uk

Mancall EL, Rosales RK 1964 Necrotising myelopathy associated with visceral carcinoma. *Brain* **87**: 639–656

Mancardi GL, Saccardi R, Filippi M *et al* 2001 Autologous hematopoietic stem cell transplantation suppresses Gd-enhanced MRI activity in MS. *Neurology* **57**: 62–68

Mancini J, Chabrol B, Moulene E, Pinsard N 1996 Relapsing acute encephalopathy: a complication of diphtheria-tetanus-poliomyelitis immunization in a young boy. *Eur J Pediatr* **155**: 135–138

Mandler RN, Davis LE, Jeffrey DR, Kormfield M 1993 Devic's neuromyelitis optica: a clinicopathological study of 8 patients. *Ann Neurol* **34**: 162–168

Mandler RN, Ahmed W, Dencoff JE 1998 Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. *Neurology* **51**: 1219–1220

Manitt C, Colicos MA, Thompson KM *et al* 2001 Widespread expression of netrin-1 by neurons and oligodendrocytes in the adult mammalian spinal cord. *J Neurosci* **21**: 3911–3922

Manley NR 2000 Thymus organogenesis and molecular mechanisms of thymic epithelial cell differentiation. *Semin Immunol* **12**: 421–428

Mann CLA, Davies MB, Boggild MD *et al* 2000 Glutathione S-transferase polymorphisms in multiple sclerosis and their relationship to disability. *Neurology* **54**: 552–557

Mann CLA, Davies MB, Stevenson VL *et al* 2002 Interleukin 1 genotypes in multiple sclerosis and relationship to disease severity. *J Neuroimmunol* **129**: 197–204

Mann MB, Wu S, Rostamkhani M *et al* 2002 Association between the phenylethanol-amine N-methyltransferase gene and multiple sclerosis. *J Neuroimmunol* **124**: 101–105

Mao CC, Gancher ST, Herndon RM 1988 Movement disorders in multiple sclerosis. *Mov Disord* **3**: 109–116

Mao Z, Bonni A, Xia F *et al* 1999 Neuronal activity-dependent cell survival mediated by transcription factor MEF2. *Science* **286**: 785–790

Mao-Draayer Y, Panitch H 2004 Alexia without agraphia in multiple sclerosis: case report with magnetic resonance imaging localization. *Mult Scler* **10**: 705–707

Marburg O 1906 Die sogennante 'akute multiple sklerose'. *Jahrb Psychiatr Neurol* **27**: 211–312

Marburg O 1936 Multiple Sklerose. In: Bumke, Förster (eds) *Handbuch der Neurologie*, Vol 13, p. 546–693

Marcao AM, Wiest R, Schindler K *et al* 2005 Adult onset metachromatic leukodystrophy without electroclinical peripheral nervous system involvement: a new mutation in the ARSA gene. *Arch Neurol* **62**: 309–313

Marchioni E, Marinou-Aktipi K, Uggetti C *et al* 2002 Effectiveness of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis. *J Neurol* **249**: 100–104

Marcos MM, Walsh EC, Ke X *et al* 2005 A high resolution linkage disequilibrium map of the human major histocompatibility complex and first generation of tag single nucleotide polymorphisms. *Am J Hum Genet* **76**: 634–646

Mariani C, Farina E, Cappa SF *et al* 1991 Neuropsychological assessment in multiple sclerosis: a follow-up study with magnetic resonance imaging. *J Neurol* **238**: 395–400

Marie P 1884 Sclérose en plaques et maladies infectieuses. *Progrès Med* **12**: 287–289, 305–307, 349–351, 365–366

Marie P 1895 *Lectures on Diseases of the Spinal Cord*. London: New Sydenham Society, pp. 102–153

Marie P, Chatelin C 1917 Sur certains symptômes d'origine vraisemblablement radiculaire, chez les blessés du crâne. *Rev Neurol* **24ii**: 336

Marine J-C, Topham DJ, Mckay C *et al* 1999 SOCS1 deficiency causes a lymphocyte

dependent perinatal lethality. *Cell* **98**: 609–616
Marinesco G 1919 Etude sur l'origine et la nature de la sclérose en plaques. *Rev Neurol* **26**: 481–488
Markovic M, Trajkovic V, Drulovic J *et al* 2003 Antibodies against myelin oligodendrocyte glycoprotein in the cerebrospinal fluid of multiple sclerosis patients. *J Neurol Sci* **211**: 67–73
Markovic-Plese S, Fukaura H, Zhang J *et al* 1995 T cell recognition of immunodominant and cryptic proteolipid protein epitopes in humans. *J Immunol* **155**: 982–992
Markovic-Plese S, Bielekova B, Kadom N *et al* 2002 Longitudinal magnetic resonance imaging study on the effect of azathioprine in relapsing–remitting multiple sclerosis patients refractory to the treatment with interferon beta-1b. *Neurology* **58**: A492
Marrie RA, Wolfson C 2001 Multiple sclerosis and varicella zoster virus infection: a review. *Epidemiol Infect* **127**: 315–325
Marrie RA, Wolfson C, Sturkenboom MC *et al* 2000 Multiple sclerosis and antecedent infections: a case–control study. *Neurology* **54**: 2307–2310
Marrosu MG, Muntoni F, Murru MR *et al* 1988 Sardinian multiple sclerosis is associated with HLA-DR4: a serologic and molecular analysis. *Neurology* **38**: 1749–1753
Marrosu MG, Muntoni F, Murru MR *et al* 1992 HLA-DQB1 genotype in Sardinian multiple sclerosis: evidence for a key role of DQB1.0201 and DQB1.0302 alleles. *Neurology* **42**: 883–886
Marrosu MG, Fadda E, Mancosu C *et al* 2000a The contribution of HLA to multiple sclerosis susceptibility in Sardinian affected sibling pairs. *Ann Neurol* **47**: 411–412
Marrosu MG, Schirru L, Fadda E *et al* 2000b ICAM-1 gene is not associated with multiple sclerosis in Sardinian patients. *J Neurol* **247**: 677–680
Marrosu MG, Murru R, Murru MR *et al* 2001 Dissection of the HLA association with multiple sclerosis in the founder isolated population of Sardinia. *Hum Mol Genet* **10**: 2907–2916
Marrosu MG, Lai M, Cocco E *et al* 2002a Genetic factors and the founder effect explain familial MS in Sardinia. *Neurology* **58**: 283–288
Marrosu MG, Cocco E, Lai M *et al* 2002b Patients with multiple sclerosis and risk of type-1 diabetes mellitus in Sardinia, Italy: a cohort study. *Lancet* **349**: 1461–1465
Marrosu MG, Sardu C, Cocco E *et al* 2004 Bias in parental transmission of the HLA-DR3 allele in Sardinian multiple sclerosis. *Neurology* **63**: 1084–1086
Mars LT, Laloux V, Goude K *et al* 2002 Va14-Ja281 NKT cells naturally regulate experimental autoimmune encephalomyelitis in nonobese diabetic mice. *J Immunol* **168**: 6007–6011
Marsden CD, Merton PA, Morton HB 1980 Maximal twitches from stimulation of the motor cortex in man. *J Physiol* **312**: 5P
Marsden CD, Obeso JA, Lang AE 1982 Adrenoleukomyeloneuropathy presenting as spinocerebellar degeneration. *Neurology* **32**: 1031–1032
Marsh SGE, Albert ED, Bodmer WF *et al* 2002 Nomenclature for factors of the HLA system, 2002. *Tissue Antigens* **60**: 407–464
Marshall EK 1948 Clinical therapeutic trial of the new drug. *Bull Johns Hopkins Hosp* **85**: 221–230
Marshall J 1955 Spastic paraplegia of middle age. *Lancet* **i**: 643–646
Martell M, Marcadet A, Strominger J *et al* 1987 T cell receptor alpha genes might be involved in multiple sclerosis genetic susceptibility. C*R Acad Sci* **304**: 105–110
Martin D, Near SL 1995 Protective effect of the interleukin-1 receptor antagonist (IL-1ra) on experimental allergic encephalomyelitis in rats. *J Neuroimmunol* **61:** 241–245
Martin R, Jaraquemada D, Flerlage M *et al* 1990 Fine specificity and HLA restriction of myelin basic protein-specific cytotoxic T cell lines from multiple sclerosis patients and healthy individuals. *J Immunol* **145**: 540–548
Martin R, Howell MD, Jaraquemada D *et al* 1991 A myelin basic protein peptide is recognized by cytotoxic T cells in the context of four HLA-DR types associated with multiple sclerosis. *J Exp Med* **173**: 19–24
Martin R, McFarland HF, McFarlin DE 1992a Immunological aspects of demyelinating diseases. *Annu Rev Immunol* **10**: 153–187
Martin R, Utz U, Coligan JE *et al* 1992b Diversity in fine specificity and T cell receptor usage of the human $CD4^+$ cytotoxic T cell response specific for the immunodominant myelin basic protein peptide 87–106. *J Immunol* **148**: 1359–1366
Martinelli V, Comi G, Filippi M *et al* 1991 Paraclinical tests in acute-onset optic neuritis: basal data and results of a short follow-up. *Acta Neurol Scand* **84**: 231–236
Martiney JA, Rajan AJ, Charles PC *et al* 1998 Prevention and treatment of experimental autoimmune encephalomyelitis by CNI-1493, a macrophage-deactivating agent. *J Immunol* **160**: 5588–5595
Martinez-Caceres EM, Barrau MA, Brieva L *et al* 2002 Treatment with methylprednisolone in relapses of multiple sclerosis patients: immunological evidence of immediate and short-term but not long-lasting effects. C*lin Exp Immunol* **127**: 165–171
Martinez-Naves E, Victoria-Gutierrez M, Lopez-Larrea C 1993 The germline repertoire of T cell receptor beta chain genes in multiple sclerosis patients from Spain. *J Neuroimmunol* **47**: 9–14
Martinez-Yelamos A, Saiz A, Sanchez-Valle R *et al* 2001 14–3–3 protein in the CSF as a prognostic marker in early multiple sclerosis. *Neurology* **57**: 722–724
Martins Silva B, Thorlacius T, Benediktsson K *et al* 2003 A whole genome association study in multiple sclerosis patients from north Portugal. *J Neuroimmunol* **143**: 116–119
Martyn CN, Kean D 1988 The one-and-a-half syndrome: clinical correlation with a pontine lesion demonstrated by nuclear magnetic resonance imaging in a case of multiple sclerosis. *Br J Ophthalmol* **72**: 515–517
Martyn CN, Cruddas M, Compston DAS 1993 Symptomatic Epstein–Barr virus infection and multiple sclerosis. *J Neurol Neurosurg Psychiatry* **56**: 167–168
Masdeu JC, Quinto C, Olivera C *et al* 2000 Open-ring imaging sign: highly specific for atypical brain demyelination. *Neurology* **54**: 1427–1433
Mason D 1991 Genetic variation in the stress response: susceptibility to experimental allergic encephalomyelitis and implications for human inflammatory disease. *Immunol Today* 12: 57–60
Mason JL, Goldman JE 2002 A2B5+ and O4+ Cycling progenitors in the adult forebrain white matter respond differentially to PDGF-AA, FGF-2, and IGF-1. *Mol Cell Neurosci* **20**: 30–42
Mason JL, Suzuki K, Chaplin DD, Matsushima GK 2001 Interleukin-1beta promotes repair of the CNS. *J Neurosci* **21**: 7046–7052
Mason JL, Xuan S, Dragatsis I *et al* 2003 Insulin-like growth factor (IGF) signaling through type 1 IGF receptor plays an important role in remyelination. *J Neurosci* **23**: 7710–7718
Mason JL, Toews A, Hostettler JD *et al* 2004 Oligodendrocytes and progenitors become progressively depleted within chronically demyelinated lesions. *Am J Pathol* **164**: 1673–1682
Mason JL, Angelastro JM, Ignatovoa TN *et al* 2005 ATF5 regulates the proliferation and differentiation of oligodendrocytes. *Mol Cell Neurosci* **29**: 372–380
Mason WP, Graus F, Lang B *et al* 1997 Small cell lung cancer, paraneoplastic cerebellar degeneration and the Lambert–Eaton myasthenic syndrome. *Brain* **120**: 1279–1300
Massacesi L, Parigi A, Barilaro A *et al* 2000 MRI Evaluation of azathioprine activity on encephalic lesions in relapsing–remitting multiple sclerosis. *Neurology* **54**: A16–A17
Massaro AR, Michetti F, Laudison A, Bergonzi P 1985 Myelin basic protein and S-100 antigen in cerebrospinal fluid of patients with multiple sclerosis in the acute phase. *Ital J Neurol Sci* **6**: 53–56
Massaro AR, Albrechtsen M, Bock E 1987 N-CAM in cerebrospinal fluid: a marker of synaptic remodelling after acute phases of multiple sclerosis? *Ital J Neurol Sci* **6**: 85–88
Massey JM 2003 Domestic violence in neurological practice. In: Noseworthy JH (ed.) *Neurological Therapeutics: Principles and Practice*. London: Martin Dunitz, pp. 65–68
Masterman T, Ligers A, Olsson T *et al* 2000 HLA-DR15 is associated with lower age at onset in multiple sclerosis. *Ann Neurol* **48**: 211–219
Masterman T, Ligers A, Zhang Z *et al* 2002a C*TLA*4 polymorphisms and the multiple

sclerosis phenotype. *J Neuroimmunol* **131**: 208–212
Masterman T, Zhang Z, Hellgren D *et al* 2002b APOE genotypes and disease severity in multiple sclerosis. *Mult Scler* **8**: 98–103
Mastrostefano R, Occhipinti E, Bigotti G, Pompili A 1987 Multiple sclerosis plaque simulating cerebral tumour: case report and review of the literature. *Neurosurgery* **21**: 244–246
Masucci EF, Saini N, Kurtzke JF 1989 Bilateral ballism in multiple sclerosis. *Neurology* **39**: 1941–1942
Matesanz F, Fedetz M, Collado-Romero M *et al* 2001 Allelic expression and interleukin-2 polymorphisms in multiple sclerosis. *J Neuroimmunol* **119**: 101–105
Mather FJ, Simon RM, Clark GM, Von Hoff DD 1987 Cardiotoxicity in patients treated with mitoxantrone: Southwest Oncology Group Phase II studies. *Cancer Treat Rep* **71**: 609–613
Mathew NT, Mathai KV, Abraham J, Taori GM 1971 Incidence and pattern of demyelinating disease in India. *J Neurol Sci* **13**: 27–38
Mathewson AJ, Berry M 1985 Observations on the astrocyte response to a cerebral stab wound in adult rats. *Brain Res* **327**: 61–69
Mathis C, Denisenko-Nehrbass N, Girault JA, Borrelli E 2001 Essential role of oligodendrocytes in the formation and maintenance of central nervous system nodal regions. *Development* **128**: 4881–4890
Mathisen PM, Pease S, Garvey J *et al* 1993 Identification of an embryonic isoform of myelin basic protein that is expressed widely in the mouse embryo. *Proc Natl Acad Sci USA* **90**: 10125–10129
Matias-Guiu J, Boulmar F, Martin R *et al* 1990 Multiple sclerosis in Spain: an epidemiological study of the Alcoy health region, Valencia. *Acta Neurol Scand* **81**: 479–483
Matias-Guiu J, Galiano L, Ribera C *et al* 1994 In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, p. 190
Matsuda M, Tabata K, Miki J *et al* 2001 Multiple sclerosis with secondary syringomyelia: an autopsy report. *J Neurol Sci* **184**: 189–196
Matsumoto J, Morrow D, Kaufman K *et al* 2001 Surgical therapy for tremor in multiple sclerosis – an evaluation of outcome measures. *Neurology* **57**: 1876–1882
Matsumoto Y, Abo T 1994 Lack of 'determinant spread' to the minor encephalitogenic epitope in myelin basic protein-induced acute experimental autoimmune encephalomyelitis in the rat. *Cell Immunol* **155**: 517–523
Matsumoto Y, Fujiwara M 1987 Absence of donor-type major histocompatibility complex class I antigen-bearing microglia in the rat central nervous systsem of radiation bone marrow chimeras. *J Neuroimmunol* **17**: 71–82
Matsumoto Y, Fujiwara M 1988 Adoptively transfered experimental allergic encephalomyelitis in chimeric rats: identification of transfered cells in the lesions of the central nervous system. *Immunology* **65**: 23–29
Matsumoto Y, Fujiwara M 1993 Immunomodulation of experimental autoimmune encephalomyelitis by staphylococcal enterotoxin D. *Cell Immunol* **149**: 268–278
Matsumoto Y, Kohyama K, Aikawa Y *et al* 1998 Role of natural killer cells and TCR-gd T cells in acute autoimmune encephalomyelitis. *Eur J Immunol* **28**: 1681–1688
Matsumoto Y, Yoon WK, Jee Y *et al* 2003 Complementarity-determining region 3 spectratyping analysis of the TCR repertoire in multiple sclerosis. *J Immunol* **170**: 4846–4853
Matthews JN 1995 Small clinical trials: are they all bad? *Stat Med* **14**:115–126
Matthews JR 1995 *Quantification and the Quest for Medical Certainty*. Princeton, NJ: Princeton University Press
Matthews WB 1958 Tonic seizures in disseminated sclerosis. *Brain* **81**: 193–206
Matthews WB 1962 Epilepsy and disseminated sclerosis. *Q J Med* **31**: 141–155
Matthews WB 1966 Facial myokymia. *J Neurol Neurosurg Psychiatry* **29**: 35–39
Matthews WB 1968 The neurological complications of ankylosing spondylitis. *J Neurol Sci* **6**: 561–573
Matthews WB 1975 Paroxysmal symptoms in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **38**: 617–623
Matthews WB 1979 Multiple sclerosis presenting with acute remitting psychiatric symptoms. *J Neurol Neurosurg Psychiatry* **42**: 859–863
Matthews WB 1998 Symptoms and signs of multiple sclerosis. In: Compston A, Ebers G, Lassmann H *et al* (eds) *McAlpine's Multiple Sclerosis*, 3rd edn. London: Churchill Livingstone, pp. 145–190
Matthews WB, Esiri M 1983 The migrant sensory neuritis of Wartenberg. *J Neurol Neurosurg Psychiatry* **46**: 1–4
Matthews WB, Small DG 1979 Serial recordings of visual and somatosensory evoked potentials in multiple sclerosis. *J Neurol Sci* **40**: 11–21
Matthews WB, Small DG, Small M, Pountney E 1977 Pattern evoked visual potential in the diagnosis of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **40**: 1009–1014
Matthews WB, Acheson ED, Batchelor JR, Weller RO 1985 *McAlpine's Multiple Sclerosis*, 1st edn. London: Churchill Livingstone
Matthews WB, Compston DAS, Allen IV, Martyn CN 1991 *McAlpine's Multiple Sclerosis*, 2nd edn. Edinburgh: Chuchill Livingstone
Matute C 1998 Characteristics of acute and chronic kainate excitotoxic damage to the optic nerve. *Proc Natl Acad Sci USA* **95**: 10229–10234
Matute C, Alberdi E, Domercq M *et al* 2001 The link between excitotoxic oligodendroglial death and demyelinating diseases. *Trends Neurosci* **24**: 224–230
Matysiak M, Jurewicz A, Jaskolski D, Selmaj K 2002 TRAIL induces death of human oligodendrocytes isolated from adult brain. *Brain* **125**: 2469–2480
Matyszak MK, Perry VH 1996a A comparison of leucocyte responses to heat-killed bacillus Calmette–Guerin in different CNS compartments. *Neuropathol Appl Neurobiol* **22**: 44–53
Matyszak MK, Perry VH 1996b The potential role of dendritic cells in immune-mediated inflammatory diseases in the central nervous system. *Neuroscience* **74**: 599–608
Matyszak MK, Perry VH 1996c Delayed-type hypersensitivity lesions in the central nervous system are prevented by inhibitors of matrix metalloproteinases. *J Neuroimmunol* **69**: 141–149
Matyszak MK, Townsend MJ, Perry VH 1997 Ultrastructural studies of an immune-mediated inflammatory response in the CNS parenchyma directed against a nn-CNC antigen. *Neuroscience* **78**: 549–560
Mauch E, Kornhuber HH, Knapf H, Fetzer V, Laufer H 1992 Treatment of multiple sclerosis with mitoxantrone. *Eur Arch Psychiatry Clin Neurosci* **242**: 96–102
Mauerhoff T, Pujol-Borrell R, Mirakian R, Bottazzo GF 1988 Differential expression and regulation of major histocompatibility complex (MHC) products in neural and glial cells of the human foetal brain. *J Neuroimmunol* **18**: 271–289
Maurer M, Kruse N, Giess R *et al* 1999 Gene polymorphism at position –308 of the tumor necrosis factor alpha promotor is not associated with disease progression in multiple sclerosis patients. *J Neurol* **246**: 949–954
Maurer M, Kruse N, Giess R *et al* 2000 Genetic variation at position –1082 of the interleukin 10 (IL10) promotor and the outcome of multiple sclerosis. *J Neuroimmunol* **104**: 98–100
Maurer M, Ponath A, Kruse N, Rieckmann P 2002 CTLA4 exon 1 dimorphism is associated with primary progressive multiple sclerosis. *J Neuroimmunol* **131**: 213–215
Mayr WT, Pittock SJ, McClelland RL *et al* 2003 Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota 1985–2000. *Neurology* **61**: 1373–1377
Mayr-Wohlfart U, Paulus C, Hennenberg A, Rodel G 1996 Mitochondrial DNA mutations in multiple sclerosis patients with severe optic involvement. *Acta Neurol Scand* **94**: 167–171
Mazza G, Ponsford M, Lowrey P *et al* 2002 Diversity and dynamics of the T-cell response to MBP in DR2+ve individuals. *Clin Exp Immunol* **128**: 538–547
Mazzarello P, Poloni M, Piccolo G, Cosi V, Pinelli P 1983 Intrathecal methylprednisolone acetate in multiple

sclerosis treatment. *Clinical evaluation. Acta Neurolo Belg* **83**: 190–196
Mbonda E, Larnaout A, Maertens A *et al* 1990 Multiple sclerosis in a black Cameroonian woman. *Acta Neurol Belg* **90**: 218–222
Mead RJ, Singhrao SK, Neal JW *et al* 2002 The membrane attack complex of complement causes severe demyelination associated with acute axonal injury. *J Immunol* **168**: 458–465
Mead SH, Proukakis C, Wood NW *et al* 2001 A large family with hereditary spastic paraparesis due to a frame shift mutation of the spastin (SPG4) gene: association with multiple sclerosis in two affected siblings and epilepsy in other affected family members. *J Neurol Neurosurg Psychiatry* **71**: 788–791
Meadows SP 1969 Retrobulbar and optic neuritis in childhood and adolescence. *Trans Ophthalmol Soc UK* **89**: 603–638
Meca-Lallana JE, Martin JJ, Lucas C *et al* 1999 Susac syndrome: clinical and diagnostic approach: a new case report. *Rev Neurol* **29**: 1027–1032
van der Meche FG, Schmitz PI 1992 A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. Dutch Guillain-Barré Study Group. *N Engl J Med* **326**: 1123–1129
Medaer R 1979 Does the history of multiple sclerosis go back as far as the 14th century? *Acta Neurol Scand* **60**: 189–192
Medaer R, Stinissen P, Truyen L *et al* 1995 Depletion of myelin basic protein autoreactive T cells by T-cell vaccination: pilot trial in multiple sclerosis. *Lancet* **346**: 807–808
Medana IM, Esiri MM 2003 Axonal damage: a key predictor of outcome in human CNS diseases. *Brain* **126**: 515–530
Medana IM, Gallimore A, Oxenius A *et al* 2000 MHC class I-restricted killing of neurons by virus specific CD8+ T lymphocytes is effected through the Fas/FasL, but not the perforin pathway. *Eur J Immunol* **30**: 3623–3633
Medana IM, Li ZX, Flügel A *et al* 2001a Fas ligand (CD95L) protects neurons against perforin-mediated T lymphocyte cytotoxicity. *J Immunol* **167**: 674–681
Medana IM, Martinic MA, Wekerle H, Neumann H 2001b Transection of major histocompatibility complex class I-induced neurites by cytotoxic T lymphocytes. *Am J Pathol* **159**: 809–815
Meh D, Denislic M 1998 Autonomic evaluation by means of standard tests and power spectral analysis in multiple sclerosis. *Muscle Nerve* **21**: 678–680
van der Mei IA, Ponsonby AL, Blizzard L, Dwyer T 2001 Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. *Neuroepidemiology* **20**: 168–174
van der Mei IA, Ponsonby AL, Dwyer T *et al* 2003 Past exposure to sun, skin phenotype, and the risk of multiple sclerosis: case-control study. *Br Med J* **327**: 316
Meier P, Finch A, Evan G 2000 Apoptosis in development. *Nature* **407**: 796–801
Meinl E, Weber F, Drexler K *et al* 1993 Myelin basic protein specific T lymphocyte repertoire in multiple sclerosis: complexity of response and dominance of nested epitopes due to recruitment of multiple T cell clones. *J Clin Invest* **92**: 2633–2643
Meinl E, Hoch RM, Dornmair K *et al* 1997 Encephalitogenic potential of myelin basic protein-specific T cells isolated from normal rhesus macaques. *Am J Pathol* **150**: 445–453
Mekki-Dauriac S, Agius E, Kan P, Cochard P 2002 Bone morphogenetic proteins negatively control oligodendrocyte precursor specification in the chick spinal cord. *Development* **129**: 5117–5130
Melamed D, Nemazee D 1997 Self antigen does not accelerate immature B cell apoptosis, but stimulates receptor editing as a consequence of developmental arrest. *Proc Natl Acad Sci USA* **94**: 9267–9272
Melin J, Usenius JP, Fogelholm R 1996 Left ventricular failure and pulmonary edema in acute multiple sclerosis. *Acta Neurol Scand* **93**: 315–317
Mellai M, Giordano M, D'Alfonso S *et al* 2003 Prolactin and prolactin receptor gene polymorphisms in multiple sclerosis and systemic lupus erythematosus. *Hum Immunol* **64**: 274–284
Mellars P 2004 Neanderthals and the modern human colonization of Europe. *Nature* **432**: 461–465
Mellins E, Kempin S, Smith L *et al* 1991 A gene required for class 2 restricted antigen presentation maps to the major histocompatibility complex. *J Exp Med* **174**: 1607–1615
Ménage P, de Toffol B, Degenne D, Saudeau D, Bardos P, Autret A 1993 Syndrome de Gougerot-Sjögren primitif. Atteinte neurologique centrale évoluant par poussées. *Rev Neurol* **149**: 554–556
Ménage P, Carreau V, Tourbah A *et al* 1994 Les adrénoleucodystrophies hétérozygotes symptomatiques de l'adulte: 10 cas. *Rev Neurol* **149**: 445–454
Menard A, Paranhos-Baccala G, Pelletier J *et al* 1997 A cytotoxic factor for glial cells: a new avenue of research for multiple sclerosis? *Cell Mol Biol* **43**: 889–901
Mendel I, Kerlero de Rosbo N, Ben-Nun A 1995 A myelin oligodendrocyte glycoprotein peptide induces typical chronic experimental autoimmune encephalomyelitis in H-2^b mice: fine specificity and T cell receptor Vb expression of encephalitogenic T cells. *Eur J Immunol* **25**: 1951–1959
Mendel I, Kerlero de Rosbo N, Ben-Nun A 1996 Delineation of the minimal encephalitogenic epitope within the immunodominant region of myelin oligodendrocyte glycoprotein: diverse V beta gene usage by T-cells recognizing the core epitope encephalitogenic for T-cell receptor V beta b and T cell receptor V beta a H-2b mice. *Eur J Immunol* **26**: 2470–2479
Mendel I, Katz A, Kozak N *et al* 1998 Interleukin-6 functions in autoimmune encephalomyelitis: a study in gene-targeted mice. *Eur J Immunol* **28**: 1727–1737
Mendell JR, Kolkin S, Kissel JT *et al* 1987 Evidence for central nervous system demyelination in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* **37**: 1291–1294
Menkes JH 1990 The leucodystrophies. *N Engl J Med* **322**: 54–55
Menon GJ, Thaller VT 2002 Therapeutic external ophthalmoplegia with bilateral retrobulbar botulinum toxin: an effective treatment for acquired nystagmus with oscillopsia. *Eye* **16**: 804–806
Menozzi P, Piazza A, Cavalli-Sforza L 1978 Synthetic maps of human gene frequencies in Europeans. *Science* **201**: 786–792
Menuhin Y 1996 Du Pre, Jacqueline Mary. In: CS Nicholls (ed.) *Dictionary of National Biography 1986–1990*. Oxford: Oxford University Press, pp. 114–116
Merelli E, Casoni F 2000 Prognostic factors in multiple sclerosis: role of intercurrent infections and vaccinations against influenza and hepatitis B. *Neurol Sci* **21 (Suppl)**: 853–856
Merelli E, Bedin R, Sola P *et al* 1997 Human herpes virus 6 and human herpes virus 8 DNA sequences in brains of multiple sclerosis patients, normal adults and children. *J Neurol* **244**: 450–454
Merle H, Smadja D, Merle S *et al* 2005 Visual phenotype of multiple sclerosis in the Afro-Caribbean population and the influence of migration to metropolitan France. *Eur J Ophthalmol* **15**: 392–399
Merrill JE 1992 Proinflammatory and antiinflammatory cytokines in multiple sclerosis and central nervous system acquired immunodeficiency syndrome. *J Immunother* **12**: 167–170
Merrill JE, Benveniste EN 1996 Cytokines in inflammatory brain lesions: helpful and harmful. *Trends Neurosci* **19**: 331–338
Merrill JE, Ignarro LJ, Sherman MP *et al* 1993 Microglial cell cytotoxicity of oligodendrocytes is mediated through nitric oxide. *J Immunol* **151**: 2132–2141
Merriman A, Cordell HJ, Eaves IA *et al* 2001 Suggestive evidence for association of human chromosome 18q12-q21 and its orthologue on rat and mouse chromosome 18 with several autoimmune diseases. *Diabetes* **50**: 184–194
Mertens C, Brassat D, Reboul J *et al* 1998 A systematic study of oligodendrocyte growth factors as candidates for genetic susceptibility to MS. *Neurology* **51**: 748–753
Mertin J, Rudge P, Kremer M *et al* 1982 Double blind controlled trial of immunosuppression in the treatment of multiple sclerosis: final report. *Lancet* **ii**: 351–354
Merton PA, Morton HB 1980a Stimulation of the cerebral cortex in the intact human subject. *Nature* **285**: 227

Merton PA, Morton HB 1980b Electrical stimulation of human motor and visual cortex through the scalp. *J Physiol* **305**: 9–10

Merton PA, Morton HB, Hill DK, Marsden CD 1982 Scope of a technique for electrical stimulation of the human brain, spinal cord and muscle. *Lancet* **2**: 597–600

Messersmith DJ, Murtie JC, Le TQ *et al* 2000 Fibroblast growth factor 2 (FGF2) and FGF receptor expression in an experimental demyelinating disease with extensive remyelination. *J Neurosci Res* **62**: 241–256

Metz L, Page S 2003 Oral cannabinoids for spasticity in multiple sclerosis: will attitude continue to limit use? *Lancet* **362**: 1513

Metz LM, Fritzler MJ, Seland TP 1988 Sjögren's syndrome infrequently mimics multiple sclerosis. *Can J Neurol Sci* **15**: 198

Metz LM, Sabuda D, Hilsden RJ *et al* 1999 Gastric tolerance of high-dose pulse oral prednisone in multiple sclerosis. *Neurology* **53**: 2093–2096

Metz LM, Zhang Y, Yeung M *et al* 2004 Minocycline reduces gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann Neurol* **55**: 756

Meuth SG, Budde T, Duyar H *et al* 2003 Modulation of neuronal activity by the endogenous pentapeptide QYNAD. *Eur J Neurosci* **18**: 2697–2706

Mews I, Bergmann M, Bunkowski S *et al* 1998 Oligodendrocyte and axon pathology in clinically silent multiple sclerosis lesions. *Mult Scler* **4**: 55–62

Meyer-Franke A, Kaplan MR, Pfeiger FW, Barres BA 1995 Characterisation of the signalling interactions that promote the survival and growth of developing retinal ganglion cells in culture. *Neuron* **15**: 805–819

Meyer-Rienecker H 1994 Epidemiological analyses on multiple sclerosis in the region of Rostock, north-East Germany. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 134–142

Meyer-Rienecker H, Buddenhagen F 1988 Incidence of multiple sclerosis: a periodic or stable phenomenon. *J Neurol* **235**: 241–244

MHC Sequencing Consortium 1999 Complete sequence and gene map of a human major histocompatibility complex. *Nature* **401**: 921–923

Mi S, Lee X, Shao Z *et al* 2004 LINGO-1 is a component of the Nogo-66 receptor/p75 signaling complex. *Nature Neurosci* **7**: 221–228

Mi S, Miller RH, Lee X *et al* 2005 LINGO-1 negatively regulates myelination by oligodendrocytes. *Nature Neurosci* **8**: 745–751

Micera A, Lambiase A, Rama P, Aloe L 1999 Altered nerve growth factor level in the optic nerve of patients affected by multiple sclerosis. *Mult Scler* **5**: 389–394

Michielsens B, Wilms G, Marchal G, Carton H 1990 Serial magnetic resonance imaging studies with paramagnetic contrast medium: assessment of disease activity in patients with multiple sclerosis before and after influenza vaccination. *Eur Neurol* **30**: 258–259

Middleton D, Savage DA, Cullen C *et al* 1992 Frequency of HLA-DP1 alleles in multiple sclerosis patients from northern Ireland. *Eur J Immunogenet* **19**: 323–326

Middleton D, Megaw G, Cullen C *et al* 1994 TAP1 and TAP2 polymorphisms in multiple sclerosis patients. *Hum Immunol* **40**: 131–134

Middleton LT, Dean G 1991 Multiple sclerosis in Cyprus. *J Neurol Sci* **103**: 29–36

Midgard R, Riise T, Nyland H 1991 Epidemiologic trends in multiple sclerosis in More and Romsdal, Norway: a prevalence/incident study in a stable population. *Neurology* **41**: 887–892

Midgard R, Albrektsen G, Riise T *et al* 1995 Prognostic factors for survival in multiple sclerosis: a longitudinal, population-based study in More and Romsdal, Norway. *J Neurol Neurosurg Psychiatry* **58**: 417–421

Midgard R, Riise T, Svanes C *et al* 1996a Incidence of multiple sclerosis in More and Romsdal, Norway from 1950–1991. *Brain* **119**: 203–211

Midgard R, Gronning M, Riise T *et al* 1996b Multiple sclerosis and chronic inflammatory diseases: a case-control study. *Acta Neurol Scand* **93**: 322–328

Miethke T, Wahl C, Heeg K *et al* 1992 T cell-mediated lethal shock triggered in mice by the superantigen staphylococcal enterotoxin B: critical role of tumor necrosis factor. *J Exp Med* **175**: 91–98

Mikaeloff Y, Adamsbaum C, Husson B *et al* 2004a MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. *Brain* **127**: 1942–1947

Mikaeloff Y, Suissa S, Vallée L *et al* 2004b First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. *J Pediatrics* **144**: 246–252

Milanese C, Salmaggi A, La Mantia L *et al* 1988a Intrathecal beta-interferon in multiple sclerosis (letter). *Lancet* **ii**: 563–564

Milanese C, La Mantia L, Salmagi A *et al* 1988b Double blind controlled randomised study on azathioprine efficacy in multiple sclerosis: preliminary results. *Ital J Neurol Sci* **9**: 53–57

Milanese C, Salmaggi A, La Mantia L *et al* 1990 Double blind controlled study of intrathecal beta-interferon in multiple sclerosis: clinical and laboratory results. *J Neurol Neurosurg Psychiatry* **53**: 554–557

Milanese C, La Mantia L, Salmaggi A, Eoli M 1993 A double blind study on azathioprine efficacy in multiple sclerosis: final report. *J Neurol* **240**: 295–298

Milanov I, Topalov N, Kmetski T 1999 Prevalence of multiple sclerosis in Gypsies and Bulgarians. *Neuroepidemiology* **18**: 218–222

Milea D, Napolitano M, Dechy M *et al* 2001 Complete bilateral horizontal gaze paralysis disclosing multiple sclerosis. *J Neurol Neurosurg Psychiatry* **70**: 252–255

Millar JHD, Allison RS 1971 *Multiple Sclerosis, A Disease Acquired in Childhood*. Springfield, IL: C.C. Thomas

Millar JHD, Allison RS, Cheeseman EA, Merrett JD 1959 Pregnancy as a factor influencing relapse in disseminated sclerosis. *Brain* **82**: 417–426

Millar JHD, Vas CJ, Noronha MJ *et al* 1967 Long-term treatment of multiple sclerosis with corticotropin. *Lancet* **2**: 429–431

Millar JHD, Zilkha KJ, Langman MJS *et al* 1973 Double-blind trial of linolate supplementation of the diet in multiple sclerosis. *Br Med J* **1**: 765–768

Millefiorini E, Gasperini C, Possillie C *et al* 1997 Randomized placebo-controlled trial of mitoxantrone in relapsing–remitting multiple sclerosis: 24 month clinical and MRI outcome. *J Neurol* **244**: 153–159

Miller A, Lider O, Roberts AB *et al* 1992 Suppressor T cells generated by oral tolerization to myelin basic protein suppress both the *in vitro* and *in vivo* immune responses by the release of transforming growth factor β after antigen-specific triggering. *Proc Natl Acad Sci USA* **89**: 421–425

Miller A, Lanir N, Shapiro S *et al* 1996 Immunoregulatory effects of interferon-β and interacting cytokines on human vascular endothelial cells: implications for multiple sclerosis and other autoimmune diseases. *J Neuroimmunol* **64**: 151–161

Miller AE, Morgante RN, Buchwald LY *et al* 1997 A multicentre, randomised, double-blind, placebo-controlled trial of influenza immunisation in multiple sclerosis. *Neurology* **48**: 312–314

Miller DH 1988 MRI: sensitive and safe in diagnosing multiple sclerosis. *MRI Decisions* **2**: 17–24

Miller DH 2004a Brain atrophy, interferon beta, and treatment trials in multiple sclerosis. *Lancet* **364**: 1463–1464

Miller DH 2004b Biomarkers and surrogate outcomes in neurodegenerative disease: lessons from multiple sclerosis. *NeuroRx* **1**: 284–294

Miller DH, Hornabrook RW, Dagger J, Fong R 1986a Ethnic and HLA patterns related to multiple sclerosis in Wellington, New Zealand. *J Neurol Neurosurg Psychiatry* **49**: 43–46

Miller DH, Johnson G, McDonald WI *et al* 1986b Detection of optic nerve lesions in optic neuritis with magnetic resonance imaging. *Lancet* **1**: 1490–1491

Miller DH, McDonald WI, Blumhardt LD *et al* 1987a Magnetic resonance imaging in isolated noncompressive spinal cord syndromes. *Ann Neurol* **22**: 714–723

Miller DH, Ormerod IEC, Gibson A *et al* 1987b MR brain scanning in patients with vasculitis: differentiation from multiple sclerosis. *Neuroradiology* **29**: 226–231

Miller DH, Ormerod IEC, McDonald WI *et al* 1988a The early risk of multiple sclerosis after optic neuritis. *J Neurol Neurosurg Psychiatry* **51**: 1569–1571

Miller DH, Rudge P, Johnson G *et al* 1988b Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. *Brain* **111**: 927–939

Miller DH, Newton MR, van der Poel JC *et al* 1988c Magnetic resonance imaging of the optic nerve in optic neuritis. *Neurology* **38**: 175–179

Miller DH, Kendall BE, Barter S *et al* 1988d Magnetic resonance imaging in central nervous system sarcoidosis. *Neurology* **38**: 378–383

Miller DH, Hornabrook RW, Dagger J, Fong R 1989a Class 2 antigens in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **52**: 575–577

Miller DH, Ormerod IEC, Rudge P *et al* 1989b The early risk of multiple sclerosis following acute syndromes of the brainstem and spinal cord. *Ann Neurol* **26**: 635–639

Miller DH, Hammond SR, McCloud JG, Skegg DCG 1990a Multiple sclerosis in Australia and New Zealand: are the determinants genetic or environmental? *J Neurol Neurosurg Psychiatry* **53**: 903–905

Miller DH, Robb SA, Ormerod IEC *et al* 1990b Magnetic resonance imaging of inflammatory and demyelinating white matter diseases of childhood. *Dev Med Child Neurol* **32**: 97–107

Miller DH, Barkhof F, Berry I *et al* 1991 Magnetic resonance imaging in monitoring the treatment of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **54**; 683–688

Miller DH, Hornabrook PW, Purdie G 1992a The natural history of multiple sclerosis: a regional study with some longitudinal data. *J Neurol Neurosurg Psychiatry* **55**: 341–346

Miller DH, Buchanan N, Barker G *et al* 1992b Gadolinium enhanced magnetic resonance imaging in systemic lupus erythematosus. *J Neurol* **239**: 460–464

Miller DH, Thompson AJ, Morrissey SP *et al* 1992c High dose steroids in acute relapses of multiple sclerosis: MRI evidence for a possible mechanism of therapeutic effect. *J Neurol Neurosurg Psychiatry* **55**: 450–453

Miller DH, Albert PS, Barkhof F *et al* 1996 Guidelines for using magnetic resonance techniques in monitoring the treatment of multiple sclerosis. *Ann Neurol* **39**: 6–16

Miller DH, Kesselring J, McDonald WI, Paty DW, Thompson AJ 1997 *Magnetic Resonance in Multiple Sclerosis*. Cambridge: Cambridge University Press

Miller DH, Grossman RI, Reingold SC, McFarland HF 1998 The role of magnetic resonance techniques in understanding and managing multiple sclerosis. *Brain* **121**: 3–24

Miller DH, Molyneux PD, Barker GJ *et al* 1999 Effect of interferon-beta1b on magnetic resonance imaging outcomes in secondary progressive multiple sclerosis: results of a European multicenter, randomized, double-blind, placebo-controlled trial. European Study Group on Interferon-beta1b in secondary progressive multiple sclerosis. *Ann Neurol* **46**: 850–859

Miller DH, Barkhof F, Frank JA *et al* 2002 Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. *Brain* **125**: 1676–1695

Miller DH, Khan OA, Sheremata WA *et al* 2003a A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* **348**: 15–23

Miller DH, Thompson AJ, Filippi M 2003b Magnetic resonance studies of abnormalities in the normal appearing white matter and grey matter in multiple sclerosis. *J Neurol* **250**: 1407–1419

Miller DH, Filippi M, Fazekas F *et al* 2004 The role of MRI within diagnostic criteria for multiple sclerosis: a critique. *Ann Neurol* **56**: 273–278

Miller DH, Barkhof F, Montalban X *et al* 2005 Clinically isolated syndromes suggestive of MS: part 2: non-conventional MRI, recovery processes, and management. *Lancet Neurol* **4**:341–348

Miller DJ, Asakura K, Rodriguez M 1996 Central nervous system remyelination: clinical application of basic neuroscience principles. *Brain Pathol* **6**: 331–344

Miller DM, Weinstock-Guttman B, Bethoux F *et al* 2000 A meta-analysis of methylprednisolone in recovery from multiple sclerosis exacerbations. *Mult Scler* **6**: 267–723

Miller HG, Evans MJ 1953 Prognosis in acute disseminated encephalomyelitis: with a note on neuromyelitis optica. Q *J Med* **22**: 347–379

Miller HG, Gibbons JL 1953 Acute disseminated encephalomyelitis and acute multiple sclerosis: results of treatment with ACTH. *Br Med J* **2**: 1345–1348

Miller HG, Stanton JB, Gibbons JL 1956 Parainfectious encephalomyelitis and related syndromes. Q *J Med* **25**: 427–505

Miller HG, Newell DJ, Ridley A *et al* 1961a Therapeutic trials in multiple sclerosis: preliminary report of the effects of intrathecal injection of tuberculin (PPD). *J Neurol Neurosurg Psychiat* **24**: 118–120

Miller HG, Newell DJ, Ridley A 1961b Multiple sclerosis: treatment of acute exacerbations with corticotrophin (ACTH). *Lancet* **ii**: 1120–1122

Miller HG, Simpson CA, Yeates WK 1965 Bladder dysfunction in multiple sclerosis. *Br Med J* **1**: 1265–1269

Miller HG, Cendrowski W, Shapira K 1967 Multiple sclerosis and vaccination. *Br Med J* **2**: 210–213

Miller JFAP 1961 Immunological function of the thymus. *Lancet* **2**: 748–749

Miller LG, Fahey JM 1994 Interleukin-1 modulates GABAergic and glutamatergic function in brain. *Ann NY Acad Sci* **739**: 292–298

Miller RA, Gralow 1984 The induction of Leu-1 antigen expression in human malignant and normal B cells by phorbol myristic actetate (PMA). *J Immunol* **133**: 3408–3414

Miller RH, Dinsio K, Wang R *et al* 2004 Patterning of spinal cord oligodendrocyte development by dorsally derived BMP4. *J Neurosci Res* **76**: 9–19

Miller SD, McRae BL, Vanderlugt CL *et al* 1995a Evolution of the T-cell repertoire during the course of experimental immune-mediated demyelinating diseases. *Immunol Rev* **144**: 225–244

Miller SD, Vanderlugt C, Lenschow DJ *et al* 1995b Blockade of CD28/B7–1 interaction prevents epitope spreading and clinical relapses of murine EAE. *Immunity* **3**: 739–745

Milligan NM, Compston DAS 1994 A placebo controlled trial of isoprinosine (immunovir) in the treatment of patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **57**: 164–168

Milligan NM, Newcombe R, Compston DAS 1987 A double blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis. I. Clinical effects. *J Neurol Neurosurg Psychiatry* **50**: 511–516

Mills KR, Murray NMR 1985 Corticospinal tract conduction time in multiple sclerosis. *Ann Neurol* **18**: 601–605

Milner BA, Regan D, Heron JR 1974 Differential diagnosis of multiple sclerosis by visual evoked potential recording. *Brain* **97**: 755–772

Milner MM, Ebner F, Justich E, Urban C 1990 Multiple sclerosis in chidhood: contribution of serial MRI to earlier diagnosis. *Dev Med Child Neurol* **32**: 769–777

Milner R, ffrench Constant C 1994 A developmental analysis of oligodendroglial integrins in primary cells: changes in *av* associated B subunits during differentiation. *Development* **120**: 3497–3506

Milonas I 1994 Epidemiological data of multiple sclerosis in Northern Greece. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 332–333

Mimura Y, Gotow T, Nishi T, Osame M 1994 Mechanisms of hyperpolarization induced by two cytokines, hTNF alpha and hIL-1 alpha in neurons of the mollusc, *Onchidium*. *Brain Res* **653**: 112–118

Minagar A, Sheremata WA 2000 Glossopharyngeal neuralgia and MS. *Neurology* **54**: 1368–1370

Minagar A, Jy W, Jimenez JJ *et al* 2001 Elevated plasma endothelial microparticles in multiple sclerosis. *Neurology* **56**: 1319–1324

Minagar A, Sheremata WA, Weiner WJ 2002 Transient movement disorders and multiple sclerosis. *Parkinsonism Relat Disord* **9**: 111–113

Minden SL, Schiffer RB 1990 Affective disorders in multiple sclerosis. *Arch Neurol* **47**: 98–104

Minden SL, Orav J, Schildkraut JJ 1988 Hypomanic reactions to ACTH and

prednisone treatment for multiple sclerosis. *Neurology* **38**: 1631–1634
Minderhoud JM, Zwanniken CP 1994 Increasing prevalence and incidence of multiple sclerosis: an epidemiological study in the province of Groningen, The Netherlands. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 113–121
Minderhoud JM, Leemhuis JG, Kremer J, Laban E, Smits PML 1984 Sexual disturbances arising from multiple sclerosis. *Acta Neurol Scand* **70**: 299–306
Minderhoud JM, van der Hoeven JH, Prange AJA 1988 Course and prognosis of chronic progressive multiple sclerosis. *Acta Neurol Scand* **78**: 10–15
Minneboo A, Barkhof F, Polman CH *et al* 2004 Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. *Arch Neurol* **61**: 217–221
Minton K 2001 Immune mechanisms in neurological disorders: protective or destructive? *Trends Immunol* **22**: 655–657
Minuk GY, Lewkonia RM 1986 Possible familial association of multiple sclerosis and inflammatory bowel disease. *N Engl J Med* **314**: 586
Miosge LA, Blasioli J, Blery M, Goodnow CC 2002 Analysis of an ethylnitrosourea-generated mouse mutation defines a cell intrinsic role of nuclear factor kappaB2 in regulating circulating B cell numbers. *J Exp Med* **196**: 1113–1119
Miravalle A, Roos KL 2003 Encephalitis following smallpox vaccination. *Arch Neurol* **60**: 925–928
Miretti MM, Walsh EC, Ke X *et al* 2005 A high-resolution linkage-disequilibrium map of the human major histocompatibility complex and first generation of tag single-nucleotide polymorphisms. *Am J Hum Genet* **76**: 634–646
Miró J, Peña-Sagredo JL, Beriano J, Insúa S, Leno C, Velarde R 1990 Prevalence of primary Sjögren's syndrome in patients with multiple sclerosis. *Ann Neurol* **27**: 582–584
Mirowska D, Wicha W, Czlonkowski A *et al* 2004 Increase of matrix metalloproteinase-9 in peripheral blood of multiple sclerosis patients treated with high doses of methylprednisolone. *J Neuroimmunol* **146**: 171–175
Mirsattari SM, Johnston JB, McKenna R *et al* 2001 Aboriginals with multiple sclerosis: HLA types and predominance of neuromyelitis optica. *Neurology* **56**: 317–123
Misu T, Onodera H, Fujihara K *et al* 2001 Chemokine receptor expression on T cells in blood and cerebrospinal fluid at relapse and remission of multiple sclerosis: imbalance of Th1/Th2-associated chemokine signaling. *J Neuroimmunol* **114**: 207–212
Miterski B, Jaeckel S, Epplen JT *et al* 1999 The interferon gene cluster: a candidate region for MS predisposition? *Genes Immun* **1**: 37–44
Miterski B, Eppelen JT, Poehlau D *et al* 2000 SCA2 alleles are not general predisposition factors for multiple sclerosis. *Neurogenetics* **2**: 235–236
Miterski B, Bohringer S, Klein W *et al* 2002a Inhibitors in the NfkappaB cascade comprise prime candidate genes predisposing to multiple sclerosis, especially in selected combinations. *Genes Immun* **3**: 211–219
Miterski B, Sindern E, Haupts M *et al* 2002b PTPRC (CD45) is not associated with multiple sclerosis in a large cohort of German patients. *BMC Med Genet* **16**: 3–5
Mitome M, Low HP, van den Pol A *et al* 2001 Towards the reconstruction of central nervous system white matter using neural precursor cells. *Brain* **124**: 2147–2161
Mitsunaga Y, Ciric B, VanKeulen V *et al* 2002 Direct evidence that a human antibody derived from a patient serum can promote myelin repair in a mouse model of chronic progressive demyelinating disease. *FASEB J* **16**: 1325–1327
Miura K 1911 [Discussion of paper by Nonne pp. 123–145] *Dtsch Z Nervenheilk* **41**: 146
Mix E, Olsson T, Correales J *et al* 1990 B cells expressing CD5 are increased in cerebrospinal fluid of patients with multiple sclerosis. *Clin Exp Immunol* **79**: 21–27
Miyagishi R, Niino M, Fukazawa T *et al* 2003 C-C chemokine receptor 2 gene polymorphism in Japanese patients with multiple sclerosis. *J Neuroimmunol* **145**: 135–138
Miyamoto K, Miyake S, Yamamura T 2001 A synthetic glycolipid prevents autoimmune encephalomyelitis by inducing Th2 bias of natural killer T cells. *Nature* **413**: 531–534
Miyazawa I, Fujihara K, Itoyama Y 2002 Eugène Devic (1858–1930). *J Neurol* **249**: 351–352
Miyazawa R, Hikima A, Takano Y *et al* 2001 Plasmapheresis in fulminant acute disseminated encephalomyelitis. *Brain Dev* **23**: 424–426
Moalem G, Leibowitz-Amit R, Yoles E *et al* 1999 Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nature Med* **5**: 49–55
Moalem G, Gdalyahu A, Shani Y *et al* 2000 Production of neurotrophins by activated T cells: implications for neuroprotective autoimmunity. *J Autoimmun* **15**: 331–345
Modi G, Mochan A, Modi M, Saffer D 2001 Demyelinating disorder of the central nervous system occurring in black South Africans. *J Neurol Neurosurg Psychiatry* **70**: 500–505
Modin H, Dai Y, Masterman T *et al* 2001 No linkage or association of the nitric oxide synthase genes to multiple sclerosis. *J Neuroimmunol* **119**: 95–100
Modin H, Masterman T, Thorlacius T *et al* 2003 Genome-wide linkage screen of a consanguineous multiple sclerosis kinship. *Mult Scler* **9**: 128–134
Modrego Pardo PJ, Pina Latorre MA, Lopez A, Errea JM 1997 Prevalence of multiple sclerosis in the province of Teruel, Spain. *J Neurol* **244**: 182–185
Modrego Pardo PJ, Pina MA 2003 Trends in prevalence and incidence of multiple sclerosis in Bajo Aragon, Spain. *J Neurol Sci* **216**: 89–93
Moen T, Stein R, Bratlie A, Bindervik E 1984 Distribution of HLA SB antigens in multiple sclerosis. *Tissue Antigens* **24**: 126–127
Moffie D 1966 De geografische vervreiding van multipele scleros. *Nederlands Tijdschr Geneeskd* **110**: 1454–1457
Mogenet I, Simiand-Erdociain E, Canonge JM, Pris J 2003 Acute myelogenous leukemia following mitoxantrone treatment for multiple sclerosis. *Ann Pharmacother* **37**: 747–748
Mogensen S (ed.) 1997 Proceedings of the 4th International Symposium on Retrovirus in Multiple Sclerosis and Related Diseases, Copenhagen, Denmark, 26 September 1996. *Acta Neurol Scand* **95 (Suppl 169)**: 1–98
Mogyoros I, Kiernan MC, Burke D, Bostock H 1997 Excitability changes in human sensory and motor axons during hyperventilation and ischaemia. *Brain* **120**: 317–325
Mogyoros I, Bostock H, Burke D 2000 Mechanisms of paresthesias arising from healthy axons. *Muscle Nerve* **23**: 310–320
Mohan N, Edwards ET, Cupps TR *et al* 2001 Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* **44**: 2862–2869
Mohlke KL, Erdos MR, Scott LJ *et al* 2002 High-throughput screening for evidence of association by using mass spectrometry genotyping on DNA pools. *Proc Natl Acad Sci USA* **99**:16928–16933
Mohr DC, Goodkin DE, Bacchetti P *et al* 2000 Psychological stress and the subsequent appearance of new brain MRI lesions in MS. *Neurology* **55**: 55–61
Mohr DC, Hart SL, Julian L *et al* 2004 Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. *Br Med J* **328**: 731
Mohr PD, Strang FA, Sambrook MA, Boddie HG 1977 The clinical and surgical features in 40 patients with primary cerebellar ectopia (adult Chiari malformation). *Q J Med* **46**: 85–96
Moins-Teisserenc H, Semana G, Alizadeh M *et al* 1995 TAP2 gene polymorphism contributes to genetic susceptibility to multiple sclerosis. *Hum Immunol* **42**: 195–202
Mojon DS, Herbert J, Sadiq SA *et al* 1999a Leber's hereditary optic neuropathy mitochondrial DNA mutations at nucleotides 11778 and 3460 in multiple sclerosis. *Ophthalmologica* **213**: 171–175
Mojon DS, Fujihara K, Hirano M *et al* 1999b Leber's hereditary optic neuropathy mitochondrial DNA mutations in familial multiple sclerosis. *Graefes Arch Clin Exp Ophthalmol* **237**: 348–350

Mokhtarian F, McFarlin DE, Raine CS 1984 Adoptive transfer of myelin basic protein-sensitized T cells produces chronic relapsing demyelinating disease in mice. *Nature* **309**: 356–358

Mokri B, Weinshenker BG, Goudreau JL *et al* 1998 Long-tract myelopathy: a novel paraneoplastic syndrome. *Ann Neurol* **44**: 486

Molina-Holgado E, Vela JM, Arevalo-Martin A, Guaza C 2001 LPS/IFN-gamma cytotoxicity in oligodendroglial cells: role of nitric oxide and protection by the anti-inflammatory cytokine IL-10. *Eur J Neurosci* **13**: 493–502

Moll C, Mourre C, Lazdunski M, Ulrich J 1991 Increase of sodium channels in demyelinated lesions of multiple sclerosis. *Brain Res* **556**: 311–316

Møller P, Hammerberg P 1963 Retinal periphlebitis in multiple sclerosis. *Acta Neurol Scand* **39 (Suppl 4)**: 263–270

Mollgard K, Saunders NR 1986 The development of the human blood brain and blood CSF barriers. *Neuropathol Appl Neurobiol* **12**: 337–358

Mollnes TE, Vandvik B, Lea T, Vartdal F 1987 Intrathecal complement activation in neurological disease evaluated by analysis of the terminal complement complex. *J Neurol Sci* **78**: 17–28

Molofsky AV, Pardal R, Iwashita T *et al* 2003 Bmi-1 dependence distinguishes neural stem cell self-renewal from progenitor proliferation. *Nature* **425**: 962–967

Moloney JBM, Masterson JG 1982 Detection of adrenoleucodystrophy carriers by means of evoked potentials. *Lancet* **ii**: 852–853

Molyneux PD, Kappos L, Polman C *et al* 2000 The effect of interferon beta-1b treatment on MRI measures of cerebral atrophy in secondary progressive multiple sclerosis. European Study Group on Interferon beta-1b in secondary progressive multiple sclerosis. *Brain* **123**: 2256–2263

Molyneux PD, Barker GJ, Barkhof F *et al* 2001 Clinical MRI correlations in a European trial of interferon beta-1b in secondary progressive MS. *Neurology* **57**: 2191–2197

Montag D, Giese KP, Bartsch V *et al* 1994 Mice deficient for the myelin associated glycoprotein gene show subtle abnormalities in myelin. *Neuron* **13**: 229–246

Montalban X 2004 Overview of European pilot study of interferon β-1b in primary progressive multiple sclerosis. *Mult Scler* **10**: S62–S64

Monteiro J, Hingorani R, Peroglizzi R *et al* 1996 Oligoclonality of $CD8^+$ T cells in multiple sclerosis. *Autoimmunity* **23**: 127–138

Montgomery SM, Lambe M, Olsson T, Ekbom A 2004 Parental age, family size, and risk of multiple sclerosis. *Epidemiology* **15**: 717–723

Montomoli C, Allemani C, Solinas G *et al* 2002a An ecologic study of geographical variation in multiple sclerosis risk in central Sardinia, Italy. *Neuroepidemiology* **21**: 187–193

Montomoli C, Prokopenko I, Caria A *et al* 2002b Multiple sclerosis recurrence risk for siblings in an isolated population of Central Sardinia, Italy. *Genet Epidemiol* **22**: 265–271

Monzani F, Caraccio N, Meucci G *et al* 1999 Effect of 1-year treatment with interferon-beta-1b on thyroid function and autoimmunity in patients with multiple sclerosis. *Eur J Endocrinol* **141:** 325–331

Monzani F, Caraccio N, Casolaro A *et* al 2000 Long-term interferon β-1b therapy for MS: is routine thyroid assessment always useful? *Neurology* **55**: 549–552

Moody DB, Porcelli SA 2001 CD1 trafficking: Invariant chain gives a new twist to the tale. *Immunity* **15**: 861–865

Moon LDF, Asher RA, Rhodes KE, Fawcett JW 2001 Regeneration of CNS axons back to their original target following treatment of adult rat brain with chondroitinase ABC. *Nat Neurosci* **4**: 465–466

Moore CEG, Lees AJ, Schady W 1996 Multiple sclerosis leading to blepharospasm and dystonia in a sibling pair. *J Neurol* **243**: 667–670

Moore FG, Andermann F, Richardson J *et al* 2001 The role of MRI and nerve root biopsy in the diagnosis of neurosarcoidosis. *Can J Neurol Sci* **28**: 349–353

Moore GR, Raine CS 1988 Immunogold localization and analysis of IgG during immune-mediated demyelination. *Lab Invest* **59**: 641–648

Moore GR, Neumann PE, Suzuki K *et al* 1985 Balo's concentric sclerosis: new observations on lesion development. *Ann Neurol* **17**: 604–611

Moore GR, Leung E, MacKay AL 2000 A pathology-MRI study of the short-T2 component in formalin-fixed multiple sclerosis brain. *Neurology* **55**: 1506–1510

Moore PM, Lisak RP 1990 Multiple sclerosis and Sjögren's syndrome: a problem of diagnosis or in definition of two disorders of unknown aetiology. *Ann Neurol* **27**: 595–596

Mor F, Cohen IR 1993 Shifts in the epitopes of myelin basic protein recognized by Lewis rat T cells before, during and after the induction of experimental autoimmune encephalomyelitis. *J Clin Invest* **92**: 2199–2206

Mor F, Cohen IR 1995 Pathogenicity of T cells responsive to diverse cryptic epitopes of myelin basic protein in the Lewis rat. *J Immunol* **155**: 3693–3699

Moreau T, Thorpe J, Miller D *et al* 1994 Preliminary evidence from magnetic resonance imaging for reduction in disease activity after lymphocyte depletion in multiple sclerosis. *Lancet* **344**: 298–301

Moreau T, Coles A, Wing M *et al* 1996 Transient increase in symptoms associated with cytokine release in patients with multiple sclerosis. *Brain* **119**: 225–237

Moreau T, Manceau E, Lucas B *et al* 2000 Incidence of multiple sclerosis in Dijon, France: a population-based ascertainment. *Neurol Res* **22**: 156–159

Moreau T, Blanc S, Riche G *et al* 2001 A pilot safety and tolerability study of interferon beta 1a in combination with azathioprine in multiple sclerosis. *Neurology* **56**: A353

Morell P 1984 *Myelin*, 2nd edn. New York: Plenum Press

Moreno H, Bueno E, Hernandez Cruz A *et al* 1995 Nitric oxide and cGMP modulate a presynaptic K+ channel in vitro. *Soc Neurosci Meeting Abstr* **209.10**

Moretti R, Torre P, Antonello RM *et al* 2000 Recurrent atrial fibrillation associated with pulse administration of high doses of methylprednisolone: a possible prophylactic treatment. *Eur J Neurol* **7**: 130

Morgan BP, Campbell AK, Compston DAS 1984 Terminal component of complement (C9) in cerebrospinal fluid of patients with multiple sclerosis. *Lancet* **ii**: 251–254

Morgan BP, Gasque P, Singhrao S, Piddlesden SJ 1997 The role of complement in disorders of the nervous system. *Immunopharmacology* **38**: 43–50

Morganti G, Naccarato S, Elian M *et al* 1984 Multiple sclerosis in the Republic of San Marino. *J Epidemiol Commun Hlth* **38**: 23–28

Morgello S 1995 Pathogenesis and classification of primary central nervous system lymphoma: an update. *Brain Pathol* **5**: 383–393

Moriabadi NF, Niewiesk S, Kruse N *et al* 2001 Influenza vaccination in MS: absence of T-cell response against white matter proteins. *Neurology* **56**: 938–943

Moriarty DM, Blackshaw AJ, Talbot PR *et al* 1999 Memory dysfunction in multiple sclerosis corresponds to juxtacortical lesion load on fast fluid-attenuated inversion-recovery MR images. *Am J Neuroradiol* **20**: 1956–1962

Morling N, Sandberg-Wollheim M, Fugger L *et al* 1992 Immunogenetics of multiple sclerosis and optic neuritis: DNA polymorphism of HLA class II genes. *Immunogenetics* **35**: 391–394

Morris JC 1868 Case of the late Dr CVW Pennock. *Am J Med Sci* **56**: 138–144

Morrissey SP, Miller DH, Kendall BE *et al* 1993a The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis: a five year follow-up study. *Brain* **116**: 135–146

Morrissey SP, Miller DH, Hermazewski R *et al* 1993b Magnetic resonance imaging of the central nervous system in Behcet's Disease. *Eur Neurol* **33**: 287–293

Morrissey SP, Borruat FX, Miller DH *et al* 1995 Bilateral simultaneous optic neuritis in adults: clinical, imaging, serological and genetic studies. *J Neurol Neurosurg Psychiatry* **58**: 70–74

Mortensen JT, Bronnum-Hansen H, Rasmussen K 1998 Multiple sclerosis and organic solvents. *Epidemiology* **9**: 168–171

Moser AB, Kreiter N, Bezman L *et al* 1999 Plasma very long chain fatty acids in 3,000 peroxisome disease patients and 29,000 controls. *Ann Neurol* **45**: 100–110

Moser HW 1995 Adenoleukodystrophy. *Curr Opin Neurol* **8**: 221–226
Moser HW 1997 Adrenoleucodystrophy: phenotype, genetics, pathogenesis, and therapy. *Brain* **120**: 1485–1508
Moser HW, Suzuki K 2002 In: Asbury AK, McKhann GM, McDonald WI *et al* (eds) *Diseases of the Nervous System, Clinical Neuroscience and Therapeutic Principles*, 3rd edn. Cambridge: Cambridge University Press
Moser HW, Moser AE, Singh I, O'Neill BP 1984 Adrenoleucodystrophy: survey of 303 cases: biochemistry, diagnosis and therapy. *Ann Neurol* **16**: 628–641
Moser HW, Moser AB, Naidu S, Bergin A 1991 Clinical aspects of adrenoleukodystrophy and adrenomyeloneuropathy. *Dev Neurosci* **13**: 254–261
Mosmann TR, Coffman RL 1989 Th1 and Th2 cells: different patterns of lymphokine secretion lead to different functional properties. *Ann Rev Immunol* **7**: 145–173
Mosmann TR, Sad S 1996 The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today* **17**: 138–145
Mossmann SS, Bronstein AM, Rudge P, Gresty MA 1985 Acquired pendular nystagmus suppressed by alcohol. *Neuroophthalmology* **13**: 99–106
Mosser J, Douar AM, Sarde CO *et al* 1993 Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. *Nature* **361**: 726–730
Mosser J, Lutz Y, Stoeckel ME *et al* 1994 The gene responsible for adrenoleucodystrophy encodes a peroxisomal membrane protein. *Hum Mol Genet* **3**: 265–271
Mossner R, Fassbender K, Kuhnen J, Schwartz A, Hennerici M 1996 Vascular cell adhesion molecule – a new approach to detect endothelial cell activation in MS and encephalitis *in vivo*. *Acta Neurol Scand* **93**: 118–122
Moster ML, Savino PJ, Sergott RC, Bosley TM, Schatz NJ 1984 Isolated sixth nerve palsies in younger adults. *Arch Ophthalmol* **102**: 1328–1330
Motomura S, Tabira T, Kuroiwa Y 1980 A clinical comparative study of multiple sclerosis and neuro-Behçet's syndrome. *J Neurol Neurosurg Psychiatry* **43**: 210–213
Mottershead JP, Schmierer K, Clemence M *et al* 2003 High field MRI correlates of myelin content and axonal density in multiple sclerosis – a post-mortem study of the spinal cord. *J Neurol* **250**: 1293–1301
Moulin DE, Foley KM, Ebers GC 1988 Pain syndromes in multiple sclerosis. *Neurology* **38**: 1830–1834
Mouren P, Tatossian A, Toga M *et al* 1966 Etude critique du syndrome hémiballique. *Encéphale* **55**: 212–274
Moxon W 1875 Eight cases of insular sclerosis of the brain and spinal cord. *Guys' Hosp Rep* **20**: 437–478
Muir D, Compston DAS 1996 Growth factor stimulation triggers apoptotic cell death in mature rat oligodendrocytes. *J Neurosci Res* **44**: 1–11
Mukherjee A, Vogt RF, Linthicum DS 1985 Measurement of myelin basic protein by radioimmunoassay in closed head trauma, multiple sclerosis and other neurological diseases. *Clin Biochem* **18**: 304–307
Mukhopadhyay G, Doherty P, Walsh FS *et al* 1994 A novel role for myelin associated glycoprotein as an inhibitor of axonal regeneration. *Neuron* **13**: 757–767
Mullen KT, Plant GT 1986 Colour and luminance vision in human optic neuritis. *Brain* **109**: 1–13
Müller E 1904 Pathologische Anatomie und Pathogenese. In: *Die Multiple Sklerose des Gehirns und Rückenmarks*. Jena: Gustav Fischer, pp. 300–344
Müller E 1910 Uber sensible Reizerscheinungen bei beginnender multipler sklerose. *Neurolisch Centralblatt* **29**: 17–20
Müller R 1949 Studies on disseminated sclerosis with special reference to symptomatology: course and prognosis. *Acta Med Scand* **222 (Suppl)**: 1–214
Müller R 1951 Course and prognosis of disseminated sclerosis in relation to age at onset. *Arch Neurol Psychiatry* **66**: 561–570
Müller R 1953 Genetic aspects of multiple sclerosis. *Arch Neurol Psychiatry* **70**: 733–740
Multiple Sclerosis. Hope through research. www.ninds.nih.gov/health_and_medical/pubs/multiple_sclerosis.htm
Multiple Sclerosis Genetics Group 1998 Clinical demographics of multiplex families with multiple sclerosis. *Ann Neurol* **43**: 530–534
Multiple Sclerosis Study Group 1990 Efficacy and toxicity of cyclosporine in chronic progressive multiple sclerosis: a randomised, double blinded, placebo controlled clinical trial. *Ann Neurol* **27**: 591–605
Mumford CJ, Compston DAS 1993 Problems with rating scales for multiple sclerosis: a novel solution – the CAMBS score. *J Neurol* **240**: 209–215
Mumford CJ, Fraser MB, Wood NW, Compston DAS 1992 Multiple sclerosis in the Cambridge health district of East Anglia. *J Neurol Neurosurg Psychiatry* **55**: 881–882
Mumford, CJ, Wood NW, Kellar-Wood HF, Thorpe J, Miller D, Compston DAS 1994 The British Isles survey of multiple sclerosis in twins. *Neurology* **44**: 11–15
Munari LM, Filippini G 2004 Lack of evidence for use of glatiramer acetate in multiple sclerosis. *Lancet Neurol* **3**: 641
Munari L, Filippini G 2005 Evidence for use of glatiramer acetate in multiple sclerosis. *Lancet Neurol* **4**: 76–77
Munari L, Lovati R, Boiko A 2004 Therapy with glatiramer acetate for multiple sclerosis. *Cochrane Database Syst Rev* **1**: CD004678
Munch M, MollerLarsen A, Christensen T *et al* 1995 B-lymphoblastoid cell lines from multiple sclerosis patients and a healthy control producing a putative new human retrovirus and Epstein–Barr virus. *Mult Scler* **1**: 78–81
Munch M, Hvas J, Christensen T *et al* 1998 A single subtype of Epstein-Barr virus in members of multiple sclerosis clusters. *Acta Neurol Scand* **98**: 395–399
Mungall AJ, Palmer SA, Sims SK *et al* 2003 The DNA sequence and analysis of human chromosome 6. *Nature* **425**: 805–811
Munger KL, Peeling RW, Hernan MA *et al* 2003 Infection with *Chlamydia pneumoniae* and risk of multiple sclerosis. *Epidemiology* **14**: 141–147
Munger KL, Zhang SM, O'Reilly E *et al* 2004 Vitamin D intake and incidence of multiple sclerosis. *Neurology* **62**: 60–65
Murakami M, Honjo T 1995 Involvement of B-1 cells in mucosal immunity and autoimmunity. *Immunol Today* **16**: 534–539
Muramatsu M, Honjo T 2001 Complex layers of genetic alteration in the generation of antibody diversity. *Trends Immunol* **22**: 66–68
Muraro PA, Leist T, Bielekova B, McFarland HF 2000 VLA-4/CD49d downregulated on primed T lymphocytes during interferon-beta therapy in multiple sclerosis. *J Neuroimmunol* **111**: 186–194
Muraro PA, Wandinger KP, Bielekova B *et al* 2003 Molecular trafficking of antigen-specific T cell clones in neurological immune-mediated disorders. *Brain* **126**: 20–31
Muraro PA, Liberati L, Bonanni L *et al* 2004 Decreased integrin gene expression in patients with MS responding to interferon-β treatment. *J Immunol* **150**: 123–131
Muraro PA, Douek DC, Packer A *et al* 2005 Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. *J Exp Med* **201**: 805–816
Murata Y, Inada K, Negi A 2000 Susac syndrome. *Am J Ophthalmol* **129**: 682–684
Muri RM, Weinberg O 1985 The clinical spectrum of internuclear ophthalmoplegia in multiple sclerosis. *Arch Neurol* **42**: 851–855
Murphy KM, Reiner SL 2003 The lineage decisions of helper T cells. *Nature Rev Immunol* **2**: 933–944
Murphy N, Confavreux C, Haas J *et al* 1998 Quality of life in multiple sclerosis in France, Germany and the United Kingdom. *J Neurol Neurosurg Psych* **65**: 460–466
Murray BJ, Apetauerova D, Scammell TE 2000 Severe acute disseminated encephalomyelitis with normal MRI at presentation. *Neurology* **55**: 1237–1238
Murray J 2005 *Multiple Sclerosis: The History of a Disease*. New York: Demos
Murray K, Dubois Dalcq M 1997 Emergence of oligodendrocytes from human neural spheres. *J Neurosci Res* **50**: 146–156
Murray NMF 1991 Magnetic stimulation of cortex: clinical applications. *J Clin Neurophysiol* **8**: 66–76
Murray PD, McGavern DB, Lin X *et al* 1998 Perforin-dependent neurologic injury in a viral model of multiple sclerosis. *J Neurosci* **18**: 7306–7314
Murray PD, McGavern DB, Sathornsumetee S, Rodgriguez M 2001 Spontaneous

remyelination following extensive demyelination is associated with improved neurological function in a viral model of multiple sclerosis. *Brain* **124**: 1403–1416

Murray RS, Brown B, Brian D, Cabirac GF 1992 Detection of coronavirus RNA and antigen in multiple sclerosis brain. *Ann Neurol* **31**: 525–533

Murray S, Bashir K, Penrice G, Womersley SJ 2004 Epidemiology of multiple sclerosis in Glasgow. *Scot Med J* **49**: 100–104

Murray TJ 1976 An unusual occurrence of multiple sclerosis in a small rural community. *Can J Neurol Sci* **3**: 192–194

Murray TJ 1985 Amantadine therapy for fatigue in multiple sclerosis. *Can J Neurol Sci* **12**: 251–254

Murray TJ, Murray SJ 1984 Characteristics of patients found not to have multiple sclerosis. *Can Med Assoc J* **131**: 336–337

Murthy SNK, Faden HS, Cohen ME, Bakshi R 2002 Acute disseminated encephalomyelitis in children. *Pediatrics* **110**: e21

Musette P, Bequet D, Delarbre C *et al* 1996 Expansion of a recurrent Vβ5.3$^+$ T cell population in newly diagnosed and untreated HLA-DR2 multiple sclerosis patients. *Proc Natl Acad Sci USA* **93**: 12461–12466

Mushlin AI, Mooney C, Grow V *et al* 1994 The value of diagnostic information to patients with suspected multiple sclerosis. *Arch Neurol* **51**: 67–72

Musial A, Eissa NT 2001 Inducible nitric-oxide synthase is regulated by the proteasome degradation pathway. *J Biol Chem* **276**: 24268–24273

Mussini JM, Hauw JJ, Escourolle R 1977 Immunofluorescence studies of intra cytoplasmatic immunoglobulin binding lymphoid cells in the central nervous system: report of 32 cases including 19 multiple sclerosis. *Acta Neuropathol* **40**: 227–232

Mutsaers SE, Carroll WM 1998 Focal accumulation of intra-axonal mitochondria in demyelination of the cat optic nerve. *Acta Neuropathol* **96**: 139–143

Mycko MP, Kowalski W, Kwinkowski M *et al* 1998a Multiple sclerosis: the frequency of allelic forms of tumor necosis factor and lymphotoxin-α. *J Neuroimmunol* **84**: 198–206

Mycko MP, Kwinkowski M, Tronczynska E *et al* 1998b Multiple sclerosis: the increased frequency of the ICAM-1 exon 6 gene point mutation genetic type K469. *Ann Neurol* **44**: 70–75

Mycko MP, Papoian R, Boschert U *et al* 2003 cDNA microarray analysis in multiple sclerosis lesions: detection of genes associated with disease activity. *Brain* **126**: 1048–1057

Myers KJ, Sprent J, Dougherty JP, Ron Y 1992 Synergy between encephalitogenic T cells and myelin basic protein-specific antibodies in the induction of experimental autoimmune encephalomyelitis. *J Neuroimmunol* **41**: 1–8

Myers LW, Ellison GW, Lucia M *et al* 1977 Swine influenza virus vaccination in patients with multiple sclerosis. *J Infect Dis* **136 (Suppl)**: S546–S554

Myers LW, Fahey JL, Moody DJ *et al* 1987 Cyclophosphamide 'pulses' in chronic progressive multiple sclerosis. *Arch Neurol* **44**: 828–832

Myers LW, Ellison GW, Merrill JE *et al* 1995 Pentoxyfilline not a promising treatment for multiple sclerosis. *Neurology* **45 (Suppl 4)**: A419

Myers LW, Ellison GW, Merrill JE *et al* 1998 Pentoxifylline is not a promising treatment for multiple sclerosis in progression phase. *Neurology* **51**: 1483–1486

Myhr KM, Raknes G, Nyland H, Vedeler C 1999a Immunoglobulin G Fc receptor (FcγR) IIA and IIB polymorphisms related to disability in MS. *Neurology* **52**: 1771–1776

Myhr KM, Riise T, Green Lilleas FE *et al* 1999b Interferon-alpha2a reduces MRI disease activity in relapsing–remitting multiple sclerosis. Norwegian Study Group on Interferon-alpha in Multiple Sclerosis. *Neurology* **52**: 1049–1056

Myhr KM, Riise T, Vedeler C *et al* 2001 Disability and prognosis in multiple sclerosis: demographic and clinical variables important for the ability to walk and awarding of disability pension. *Mult Scler* **7**: 59–65

Myhr KM, Vagnes KS, Maroy TH *et al* 2002 Interleukin-10 promoter polymorphism in patients with multiple sclerosis. *J Neurol Sci* **202**: 93–97

Nadler JP 1993 Multiple sclerosis and hepatitis B vaccination. *Clin Infect Dis* **17**: 928–929

Nagata S, Goldstein P 1995 The Fas death factor. *Science* **167**: 1449–1456

Nagra RM, Becher B, Tourtellotte WW *et al* 1997 Immunohistochemical and genetic evidence of myeloperoxidase involvement in multiple sclerosis. *J Neuroimmunol* **78**: 97–107

Naismith RT, Cross AH 2004 Does the hepatitis B vaccine cause multiple sclerosis? *Neurology* **63**: 772–773

Naito S, Namerow N, Mickey MR, Terasaki PI 1972 Multiple sclerosis: association with HL-A3. *Tissue Antigens* **2**: 1–4

Naito S, Kuroiwa T, Itoyama T *et al* 1978 HLA and Japanese MS. *Tissue Antigens* **12**: 19–24

Nakahara J, Seiwa C, Shibuya A *et al* 2003 Expression of Fc receptor for immunoglobulin M in oligodendrocytes and myelin of mouse central nervous system. *Neurosci Lett* **337**: 73–76

Nakamine H, Okano M, Taguchi Y *et al* 1991 Hematopathologic features of Epstein-Barr virus-induced human B-lymphoproliferation in mice with severe combined immunodeficiency. A model of lymphoproliferative diseases in immunocompromised patients. *Lab Invest* **65**: 389–399

Nakamura N, Nokura K, Zettsu T *et al* 2003 Neurologic complications associated with influenza vaccination: two adult cases. *Intern Med* **42**: 191–194

Nakashima I, Fujihara K, Okita N *et al* 1999 Clinical and MRI study of brain stem and cerebellar involvement in Japanese patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **67**: 153–157

Nakashima I, Fujihara K, Misu T *et al* 2000 Significant correlation between IL-10 levels and IgG indices in the cerebrospinal fluid of patients with multiple sclerosis. *J Neuroimmunol* **111**: 64–67

Nakazato T, Sato T, Nakamura T *et al* 1989 Adrenoleukodystrophy presenting as spinocerebellar degeneration. *Eur Neurol* **29**: 229–234

Namekawa M, Takiyama Y, Aoki Y *et al* 2002 Identification of GFAP gene mutation in hereditary adult-onset Alexander's disease. *Ann Neurol* **52**: 779–785

Namerow NS 1968a Circadian temperature rhythm and vision in multiple sclerosis. *Neurology* **18**: 417–422

Namerow NS 1968b Somatosensory evoked responses in multiple sclerosis patients with varying sensory loss. *Neurology* **18**: 1197–1204

Namerow NS 1972 The pathophysiology of multiple sclerosis. In: Wolfgram F, Ellison GW, Stevens JG *et al* (eds) *Multiple Sclerosis: Immunology, Virology and Ultrastructure*. New York: Academic Press, pp. 143–172

Namerow NS, Enns N 1972 Visual evoked responses in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **35**: 829–833

Namerow NS, Thompson LR 1969 Plaques, symptoms, and the remitting course of multiple sclerosis. *Neurology* **19**: 765–774

Nance PW, Shears AH, Nance DM 1989 Reflex changes induced by clonidine in spinal cord injured patients. *Paraplegia* **27**: 296–301

Narang HK, Field EJ 1973 Paramyxovirus like tubules in multiple sclerosis biopsy material. *Acta Neuropathol* **25**: 281–290

Narayana PA, Doyle TJ, Lai D, Wolinsky JS 1998 Serial proton magnetic resonance spectroscopic imaging, contrast enhanced magnetic resonance imaging, and quantitative lesion volumetry in multiple sclerosis. *Ann Neurol* **43**: 56–71

Narayanan S, Fu L, Pioro E *et al* 1997 Imaging of axonal damage in multiple sclerosis: spatial distribution of magnetic resonance imaging lesions. *Ann Neurol* **41**: 385–391

Narayanan S, DeStefano N, Francis GS *et al* 2001 Axonal metabolic recovery in multiple sclerosis patients treated with interferon beta-1b. *J Neurol* **249**: 979–986

Narciso P, Galgani S, Del Grosso B *et al* 2001 Acute disseminated encephalomyelitis as manifestation of primary HIV infection. *Neurology* **57**: 1493–1496

Narikawa K, Misu T, Fujihara K *et al* 2004 CSF chemokine levels in relapsing neuromyelitis optica and multiple sclerosis. *J Neuroimmunol* **149**: 182–186

Narod S, Johnson-Lussenburg CM, Zheng Q, Nelson R 1985 Clinical viral infections and multiple sclerosis. *Lancet* 165–166

Nash RA, Bowen JD, McSweeney PA *et al* 2003 High-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation for severe multiple sclerosis. *Blood* **102**: 2364–2372

Nasseri K, TenVoorde BJ, Ader HJ *et al* 1998 Longitudinal follow-up of cardiovascular reflex tests in multiple sclerosis. *J Neurol Sci* **155**: 50–54

Nataf S, Carroll SL, Wetsel RA *et al* 2000 Attenuation of experimental autoimmune demyelination in complement-deficient mice. *J Immunol* **165**: 5867–5873

Nathan MPR, Chase PH, Elguezabel A, Weinstein M 1976 Spinal cord sarcoidosis. *NY State J Med* **76**: 748–752

Nauta JJP, Thompson AJ, Barkhof F, Miller DH 1994 Magnetic resonance imaging in monitoring the treatment of multiple sclerosis patients: statistical power of parallel groups and cross-over designs. *J Neurol Sci* **122**: 6–14

Navikas V, Link H 1996 Review: cytokines and the pathogenesis of multiple sclerosis. *J Neurosci Res* **45**: 322–333

Navikas V, Link H, Palasik W *et al* 1995 Increased mRNA expression of IL-10 in mononuclear cells in multiple sclerosis and optic neuritis. *Scand J Immunol* **41**: 171–178

Navikas V, He B, Link J *et al* 1996a Augmented expression of tumour necrosis factor-α and lymphotoxin in mononuclear cells in multiple sclerosis and optic neuritis. *Brain* **119**: 213–223

Navikas V, Matusevicius D, Söderström M *et al* 1996b Increased interleukin 6 mRNA expression in blood and cerebrospinal fluid mononuclear cells in multiple sclerosis. *J Neuroimmunol* **64**: 63–69

Ndhlovu LC, Ishii N, Murata K *et al* 2001 Critical involvement of OX40 ligand signals in the T cell priming events during experimental autoimmune encephalomyelitis. *J Immunol* **167**: 2991–2999

Nedergaard M 1994 Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. *Science* **263**: 1768–1771

Nehls M, Kyewski B, Messerle M *et al* 1996 Two genetically separable steps in the differentiation of thymic epithelium. *Science* **272**: 886–889

Neilley LK, Goodin DS, Goodkin DE, Hauser SL 1996 Side effect profile of interferon beta-1b in MS: results of an open label trial. *Neurology* **46**: 552–554

Nelissen I, Fiten P, Vandenbroeck K *et al* 2000 PECAM1, MPO and PRKAR1A at chromosome 17q21-q24 and susceptibility for multiple sclerosis in Sweden and Sardinia. *J Neuroimmunol* **108**: 153–159

Nelissen I, Dubois B Goris A *et al* 2002 Gelatinase B, PECAM-1 and MCP-3 gene polymorphisms in Belgian multiple sclerosis. *J Neurol Sci* **200**: 43–48

Nellerman LJ, Frederiksen J, Morling N 1995 PCR typing of two short tandem repeat (STR) structures upstream of the human myelin basic protein (MBP) gene: the genetic susceptibility in multiple sclerosis and monosymptomatic idiopathic optic neuritis in Danes. *Mult Scler* **1**: 186–198

Nelson DA, Jeffries WH, McDowell F 1958 Effects of induced hyperthermia on some neurological diseases. *Arch Neurol Psychiatry* **79**: 31–39

Nelson LM, Anderson DW 1995 Case finding for epidemiological surveys of multiple sclerosis in United States communities. *Mult Scler* **1**: 48–55

Nelson LM, Hamman RF, Thompson HM *et al* 1986 Higher than expected prevalence of multiple sclerosis (MS) in northern Colorado: dependence on methodologic issues. *Neuroepidemiology* **5**: 17–28

Nelson LM, Franklin GM, Jones MC, and the Multiple Sclerosis Study Group 1988 Risk of multiple sclerosis exacerbation during pregnancy and breast-feeding. *J Am Med Assoc* **259**: 3441–3443

Nemazee D 2000 Receptor selection in B and T lymphocytes. *Annu Rev Immunol* **18**: 19–51

Nepom GT 2002 Therapy of autoimmune diseases: clinical trials and new biologics. *Curr Opin Immunol* **14**: 812–815

Nery S, Wichterle H, Fishell G 2001 Sonic hedgehog contributes to oligodendrocyte specification in the mammalian forebrain. *Development* **128**: 527–540

Nesbit GM, Forbes GS, Scheithauer BW *et al* 1991 Multiple sclerosis: histopathologic and MR and/or CT correlation in 37 cases at biopsy and three cases at autopsy. *Radiology* **180**: 467–474

Ness JK, Mitchell NE, Wood TL 2002 IGF-1 and NT-3 signaling pathways in developing oligodendroctyes: differential regulation and activation of receptors and the downstream effector Akt. *Dev Neurosci* **24**: 437–445

Ness JK, Scaduto RC Jr, Wood TL 2004 IGF-I prevents glutamate-mediated bax translocation and cytochrome C release in O4+ oligodendrocyte progenitors. *Glia* **46**: 183–194

Neu I, Mallinger J, Wildfeuer A, Mehlber L 1992 Leukotriene in the cerebrospinal fluid of multiple sclerosis patients. *Acta Neurol Scand* **86**: 586–587

Neuhaus O, Hartung HP 2001 In search of a disease marker: the cytokine profile of primary progressive multiple sclerosis. *Mult Scler* **7**: 143–144

Neuhaus O, Farina C, Yassouridis A *et al* 2000 Multiple sclerosis: comparison of copolymer-1- reactive T cell lines from treated and untreated subjects reveals cytokine shift from T helper 1 to T helper 2 cells. *Proc Natl Acad Sci USA* **97**: 7452–7457

Neuhaus O, Farina C, Wekerle H, Hohlfeld R 2001 Mechanisms of action of glatiramer acetate in multiple sclerosis. *Neurology* **56**: 702–708

Neuhaus O, Strasser-Fuchs S, Fazekas F *et al* 2002 Statins as immunomodulators: comparison with interferon-beta 1b in MS. *Neurology* **59**: 990–997

Neuhaus O, Stuve O, Zamvil SS, Hartung H 2004 Are statins a treatment option for multiple sclerosis? *Lancet* **3**: 369–371

Neumann H, Cavalie A, Jenne DE, Wekerle H 1995 Induction of MHC class I genes in neurons. *Science* **269**: 549–552

Neumann H, Boucraut J, Hahnel C *et al* 1996 Neuronal control of MHC class II inducibility in rat astrocytes and microglia. *Eur J Neurosci* **8**: 2582–2590

Neumann H, Schmidt H, Cavalie A *et al* 1997 MHC class I gene expression in single neurons of the central nervous system: differential regulation by interferon-γ and tumor necrosis factor-α. *J Exp Med* **185**: 305–316

Neumann H, Medana I, Bauer J, Lassmann H 2002 Cytotoxic T lymphocytes in autoimmune and degenerative CNS diseases. *Trends Neurosci* **25**: 313–319

Neumann JW, Ziegler DK 1972 Therapeutic trial of immunosuppressive agents in multiple sclerosis. *Neurology* **22**: 1268–1271

Neusch C, Rozengurt N, Jacobs RE *et al* 2001 Kir4.1 potassium channel subunit is crucial for oligodendrocyte development and in vivo myelination. *J Neurosci* **21**: 5429–5438

Newcombe J, Cuzner ML 1993 Organization and research applications of the UK Multiple Sclerosis Society tissue bank. *J Neural Transm* **39 (Suppl)**: 155–163

Newcombe J, Hawkins CP, Henderson CL *et al* 1991 Histopathology of multiple sclerosis lesions detected by magnetic resonance imaging in unfixed postmortem central nervous system tissue. *Brain* **114**: 1013–1023

Newcombe J, Li H, Cuzner ML 1994 Low density lipoprotein uptake by macrophages in multiple sclerosis plaques: implications for pathogenesis. *Neuropathol Appl Neurobiol* **20**: 152–162

Newman AK 1875 On insular sclerosis of the brain and spinal cord. *Aust Med J* **20**: 369–374

Newman EA 1986 High potassium conductance in astrocyte endfeet. *Science* **233**: 453–454

Newman PK, Saunders M 1989 Clinical aspects of methylprednisolone in multiple sclerosis. In: Capildeo R (ed.) *Steroids in Diseases of the Central Nervous System*. Chichester: Wiley, pp. 197–206

Newman PK, Saunders M, Tilley PJB 1982 Methylprednisolone therapy in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **45**: 941–942

Newman TA, Woolley ST, Hughes PM *et al* 2001 T-cell- and macrophage-mediated axon damage in the absence of a CNS-specific immune response: involvement of metalloproteinases. *Brain* **124**: 2203–2214

Ng J, Frith R 2002 Nanging. *Lancet* **360**: 384

Nguyen D, Stangel M 2001 Expression of the chemokine receptors CXCR1 and CXCR2 in rat oligodendroglial cells. *Devl Brain Res* **128**: 77–81

Nguyen JP, Degos JD 1993 Thalamic stimulation and proximal tremor: a specific target in the nucleus ventromedialis thalami. *Arch Neurol* **50**: 498–500

Nguyen KB, McCombe PA, Pender MP 1994 Macrophage apoptosis in the central nervous system in experimental autoimmune encephalomyelitis. *J Autoimmun* **7**: 145–152

Nguyen KB, Pender MP 1998 Phagocytosis of apoptotic lymphocytes by oligodendrocytes in experimental autoimmune encephalomyelitis. *Acta Neuropathol* **95**: 40–46

Nguyen KB, McCombe PA, Pender MP 1997 Increased apoptosis of T lymphocytes and macrophages in the central and peripheral nervous systems of Lewis rats with experimental autoimmune encephalomyelitis treated with dexamethasone. *J Neuropathol Exp Neurol* **56**: 58–69

Nicholas RS, Wing MG, Compston A 2001a Nonactivated microglia promote oligodendrocyte precursor survival and maturation through the transcription factor NF-kappa B. *Eur J Neurosci* **13**: 959–967

Nicholas RS, Compston DAS, Brown DR 2001b Inhibition of TNFα-induced NF-kB converts the metabolic effects of microglial-derived TNF-α on mouse cerebellar neurones to neurotoxicity. *J Neurochemistry* **76**: 1431–1438

Nicholas RS, Stevens S, Wing MG, Compston DAS 2002 Microglia-derived IGF-2 and CNTF prevent TNFα induced death of mature oligodendrocytes *in vitro*. *J Neuroimmunol* **124**: 36–44

Nicholas RS, Stevens S, Wing M, Compston DAS 2003a Oligodendrocyte-derived stress signals can recruit microglia *in vitro*. *NeuroReport* **14**: 1001–1005

Nicholas RS, Partridge J, Donn RP *et al* 2003b The role of the PTPRC (CD45) mutation in the development of multiple sclerosis in the North West region of the United Kingdom. *J Neurol Neurosurg Psych* **74**: 944–945

Nicholl JA, Kinrade E, Love S 1993 PCR-mediated search for herpes simplex virus DNA in sections of brain from patients with multiple sclerosis and other neurological disorders. *J Neurol Sci* **113**: 144–151

Nicholson LB, Greer JM, Sobel RA *et al* 1995 An altered peptide ligand mediates immune deviation and prevents autoimmune encephalomyelitis. *Immunity* **3**: 397–405

Nick S, Pileri P, Tongiani S *et al* 1995 T cell receptor γδ repertoire is skewed in cerebrospinal fluid of multiple sclerosis patients: molecular and functional analyses of γδ antigen-reactive clones. *Eur J Immunol* **25**: 355–363

Nico B, Frigeri A, Nicchia GP *et al* 2001 Role of aquaporin-4 water channel in the development and integrity of the blood-brain barrier. *J Cell Sci* **114**: 1297–1307

Nicoletti A, lo Bartolo ML, Lo Fermo S *et al* 2001 Prevalence and incidence of multiple sclerosis in Catania, Sicily. *Neurology* **56**: 62–66

Nicoletti A, Sofia V, Biondi R *et al* 2003 Epilepsy and multiple sclerosis in Sicily: a population-based study. *Epilepsia* **44**: 1445–1448

Nicolson M, Lowis GW 2002 The early history of the Multiple Sclerosis Society of Great Britain and Northern Ireland: a socio-historical study of lay/practitioner interaction in the context of a medical charity. *Med Hist* **46**: 141–174

Niederwieser G 2000 Lethal capillary leak syndrome after a single administration of interferon beta-1b. *Neurology* **54**: 1545–1546

Niederwieser G, Bonelli RM, Kammerhuber F *et al* 2001 Intracerebral haemorrhage under interferon-beta therapy. *Eur J Neurol* **8**: 363–364

Niehaus A, Shi J, Grzenkowski M *et al* 2000 Patients with active relapsing–remitting multiple sclerosis synthesize antibodies recognizing oligodendrocyte progenitor cell surface protein: implications for remyelination. *Ann Neurol* **48**: 362–371

Nielsen JF, Sinkjaer T, Jakobsen J 1996 Treatment of spasticity with repetitive magnetic stimulation: a double-blind placebo-controlled study. *Mult Scler* **2**: 227–232

Nieto M, Schuurmans C, Britz O, Guillemot F 2001 Neural bHLH genes control the neuronal versus glial fate decision in cortical progenitors. *Neuron* **29**: 401–413

Niino M, Kikuchi S, Fukazawa T *et al* 2000a Estrogen receptor gene polymorphism in Japanese patients with multiple sclerosis. *J Neurol Sci* **179**: 70–75

Niino M, Fukazawa T, Yabe T *et al* 2000b Vitamin D receptor gene polymorphism in multiple sclerosis and the association with HLA class II alleles. *J Neurol Sci* **177**: 65–71

Niino M, Kikuchi S, Fukazawa T *et al* 2001a Heat shock protein 70 gene polymorphism in Japanese patients with multiple sclerosis. *Tissue Antigens* **58**: 93–96

Niino M, Kikuchi S, Fukazawa T *et al* 2001b Genetic polymorphisms of IL-1β and IL-1 receptor antagonist in association with multiple sclerosis in Japanese patients. *J Neuroimmunol* **118**: 295–299

Niino M, Kikuchi S, Miyagishi R *et al* 2002a An examination of the association between β_2 adrenergic receptor polymorphisms and multiple sclerosis. *Mult Scler* **8**: 475–478

Niino M, Kikuchi S, Fukazawa T *et al* 2002b No association of vitamin D-binding protein gene polymorphisms in Japanese patients with MS. *J Neuroimmunol* **127**: 177–179

Niino M, Kikuchi S, Fukazawa T *et al* 2003a Genetic polymorphisms of osteopontin in association with multiple sclerosis in Japanese patients. *J Neuroimmunol* **136**: 125–129

Niino M, Kikuchi S, Fukazawa T *et al* 2003b Polymorphisms of apolipoprotein E and Japanese patients with multiple sclerosis. *Mult Scler* **9**: 382–386

Nikoskelainen E 1975 Symptoms, signs and early course of optic neuritis. *Acta Ophthalmol* **53**: 254–272

Nikoskelainen E, Riekkenen P 1974 Optic neuritis: a sign of multiple sclerosis or other diseases of the central nervous system. *Acta Neurol Scand* **50**: 690–710

Nikoskelainen E, Sogg RL, Rosenthal AR, Friberg TR, Dorfman LJ 1977 The early phase in Leber hereditary optic atrophy. *Arch Ophthalmol* **95**: 969–978

Nilsson P, Larsson EM, Maly-Sundgren P *et al* 2005 Predicting the outcome of optic neuritis: evaluation of risk factors after 30 years of follow-up. *J Neurol* **252**: 396–402

Nimmerjahn A, Kirchhoff F, Helmchen F 2005 Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science* **308**: 1314–1318

Ninfo V, Rizzutto N, Terzian H 1967 Assoziazione anatomo-clinical di nevrite ipertrofica e sclerosi a placche. *Acta Neurol* **22**: 228–237

Nishimura M, Obayashi H, Ohta M *et al* 1995 No association of the 11778 mitochondrial DNA mutation and multiple sclerosis in Japan. *Neurology* **45**: 1333–1334

Nishiyama A, Lin XH, Giese N *et al* 1996 Co-localization of NG2 proteoglycan and PDGF alpha-receptor on O2A progenitor cells in the developing rat brain. *J Neurosci Res* **43**: 299–314

Nisipeanu P, Korczyn AD 1993 Psychological stress as risk factor for exacerbations in multiple sclerosis. *Neurology* **43**: 1311–1312

Nistor GI, Totoiu MO, Haque N *et al* 2005 Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. *Glia* **49**: 385–396

Nitsch R, Pohl EE, Smorodchenko A *et al* 2004 Direct impact of T cells on neurons revealed by two-photon microscopy in living brain tissue. *J Neurosci* **24**: 2458–2464

Niu MT, Davis DM, Ellenberg S 1996 Recombinant Hepatitis B vaccination of neonates and infants: emerging safety data from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* **15**: 771–776

Nixon C, McSweeny 1893 Diffuse cerebro-spinal sclerosis. *Dublin J Med Sci* **95**: 71–72

Nobile-Orazio E, Cappellari A, Meucci N *et al* 2002 Multifocal motor neuropathy: clinical and immunological features and response to IVIg in relation to the presence and degree of motor conduction block. *J Neurol Neurosurg Psychiatry* **72**: 761–766

Noble PG, Antel JP, Yong VW 1994 Astrocytes and catalase prevent the toxicity of catecholamines to oligodendrocytes. *Brain Res* **633**: 83–90

Nonaka T, Honmou O, Sakai J *et al* 2000 Excitability changes of dorsal root axons following nerve injury: implications for injury-induced changes in axonal Na+ channels. *Brain Res* **859**: 280–285

Nonne M, Holzmann W 1911 Seroligisches zür multiplen Sklerose Speziel uber die Cobrareaktion bei der multiplen Sklerose. *Dtsch Z Nerven* **41**: 123–145

van den Noort S, Eidelman B, Rammohan K *et al* 1998 *National MS Society Clinical Bulletin: Disease Management Consensus Statement*. New York: National MS Society

Nordenbo AM, Andersen JR, Andersen JT 1996 Disturbances of ano-rectal function in multiple sclerosis. *J Urol* **243**: 445–451

Nordin M, Nyström B, Wallin U, Hagbarth K-E 1984 Ectopic sensory discharges and paraesthesiae in patients with disorders of peripheral nerves, dorsal roots and dorsal columns. *Pain* **20**: 231–245

Norman JE, Kurtzke JF, Beebe GW 1983 Epidemiology of multiple sclerosis in US veterans. 2. Latitude, climate and the risk of MS. *J Chron Dis* **36**: 551–559

Noronha A, Toscas A, Jensen MA 1993 Interferon beta-1b decreases T cell activation and interferon γ production in multiple sclerosis. *Neurology* **43**: 655–661

Noronha ABC, Richman DP, Arnason BGW 1980 Detection of *in vivo* stimulated cerebrospinal fluid lymphocytes by flow cytometry in patients with multiple sclerosis. *N Engl J Med* **303**: 713–717

Noronha MJ, Vas CJ, Aziz H 1968 Autonomic dysfunction (sweating responses) in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **31**: 19–22

Norstrand IF, Craelius 1989 A trial of deforoxamine (Desferl) in the treatment of multiple sclerosis: a pilot study. *Clin Trials J* **26**: 365–369

Norton WT, Cammer W 1984 Chemical pathology of diseases involving myelin. In: Morrell P (ed.) *Myelin*. New York: Plenum Press, pp. 369–404

Nos C, Comabella M, Tintore M *et al* 1996 High dose intravenous immunoglobulin does not improve abnormalities in the blood-brain barrier during acute relapse of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **61**: 418

Nos C, Sastre-Garriga J, Borràs C *et al* 2004 Clinical impact of intravenous methylprednisolone in attacks of multiple sclerosis. *Mult Scler* **10**: 413–416

Noseworthy JH, Hartung HP 2003 Multiple sclerosis and related conditions. In: Noseworthy JH (ed.) *Neurological Therapeutics: Principles and Practice*. London: Martin Dunitz

Noseworthy JH, Paty D, Wonnacott T *et al* 1983 Multiple sclerosis after age of 50. *Neurology* **33**: 1537–1544

Noseworthy JH, Bass BH, Vandervoort MK *et al* 1989a The prevalence of primary Sjögren's syndrome in a multiple sclerosis population. *Ann Neurol* **25**: 195–198

Noseworthy JH, Vandervoort MK, Hopkins M, Ebers GC 1989b A referendum on clinical trial research in multiple sclerosis: the opinion of the participants at the Jekyll Island workshop. *Neurology* **39**: 977–981

Noseworthy JH, Vandenvoort MK, Wong CJ, Ebers GC 1990 Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) in a multiple sclerosis clinical trial. The Canadian Cooperation MS Study Group. *Neurology* **40**: 971–975

Noseworthy JH, Hopkins MB, Vandervoort MK *et al* 1993 An open-trial evaluation of mitoxantrone in the treatment of progressive MS. *Neurology* **43**: 1401–1406

Noseworthy JH, Ebers GC, Vandervoort MK *et al* 1994 The impact of blinding on the results of a randomised, placebo-controlled multiple sclerosis clinical trial. *Neurology* **44**: 16–20

Noseworthy JH, O'Brien P, the Mayo Clinic–Canadian Cooperative MS Study Group 1998 The Mayo Clinic–Canadian Cooperative Trial of sulfasalazine in active multiple sclerosis. *Neurology* **51**: 1342–1352

Noseworthy JH, Lucchinetti C, Rodriguez M *et al* 2000a Multiple sclerosis. *N Engl J Med* **343**: 938–952

Noseworthy JH, O'Brien PC, Weinshenker BG *et al* 2000b IV immunoglobulin does not reverse established weakness in MS. *Neurology* **55**: 1135–1143

Noseworthy JH, Wolinsky JS, Lublin FD *et al* 2000c Linomide in relapsing and secondary progressive MS: part I: trial design and clinical results. North American Linomide Investigators. *Neurology* **54**: 1726–1733

Noseworthy JH, O'Brien PC, Petterson TM *et al* 2001 A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. *Neurology* **56**: 1514–1522

Noseworthy JH, Kappos L, Daumer M 2003 Competing interest in multiple sclerosis research. *Lancet* **361**: 350

Nossal GJV 2001 A purgative mastery. *Nature* **412**: 685–686

Novakovic SD, Deerinck TJ, Levinson SR *et al* 1996 Clusters of axonal Na+ channels adjacent to remyelinating Schwann cells. *J Neurocytol* **25**: 403–412

Novakovic SD, Levinson SR, Schachner M, Shrager P 1998 Disruption and reorganization of sodium channels in experimental allergic neuritis. *Muscle Nerve* **21**: 1019–1032

Nowak DA, Widenka DC 2001 Neurosarcoidosis: a review of its intracranial manifestations. *J Neurol* **248**: 363–372

Nyffeler T, Stabba A, Sturzenegger M 2003 Progressive myelopathy with selective involvement of the lateral and posterior columns after inhalation of heroin vapour. *J Neurol* **250**: 496–498

Nyland H, Mork S, Matre R 1982 In-situ characterization of mononuclear cell infiltrates in lesions of multiple sclerosis. *Neuropathol Appl Neurobiol* 8: 403–411

Nyquist PA, Cascino G, Rodriguez M 2001 Seizures in patients with multiple sclerosis seen at Mayo Clinic, Rochester, MN, 1990–1998. *Mayo Clin Proc* **76**: 983–986

Nyquist PA, Cascino GD, McClelland RL *et al* 2002 Incidence of seizures in patients with multiple sclerosis: a population-based study. *Mayo Clin Proc* **77**: 910–912

O'Brien CF 2002 Treatment of spasticity with botulinum toxin. *Clin J Pain* **18**: S182–S190

Ochs G, Struppler A, Meyerson BA *et al* 1989 Intrathecal baclofen for long-term treatment of spasticity: a multi-centre study. *J Neurol Neurosurg Psychiatry* **52**: 933–939

O'Connor KC, Appel H, Bregoli L *et al* 2005 Antibodies from inflamed central nervous system tissue recognize myelin oligodendrocyte glycoprotein. *J Immunol* **175**: 1974–1982

O'Connor PW, Goodman A, Willmer-Hulme AJ *et al* 2004 Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. *Neurology* **62**: 2038–2043

O'Duffy JD, Goldstein NP 1976 Neurologic involvement in seven patients with Behçet's syndrome. *Am J Med* **61**: 170–178

Odum N, Hyldig-Nielsen JJ, Morling N *et al* 1988 HLA-DP antigens are involved in the susceptibility to multiple sclerosis. *Tissue Antigens* **31**: 235–237

Odum N, Saida T, Ohta M, Svejgaard A 1989 HLA-DP antigens and HTLV-1 antibody status among Japanese with multiple sclerosis: evidence for an increased frequency of HLA-DPw4. *J Immunogenet* **16**: 467–473

Oehmichen M, Gruninger H, Wietholter H, Gencic M 1979 Lymphatic efflux of intracerebrally injected cells. *Acta Neuropathol* **45**: 61–65

Oehmichen M, Domasch D, Wietholter H 1982 Origin, proliferation, and fate of cerebrospinal fluid cells: a review on cerebrospinal fluid cell kinetics. *J Neurol* **227**: 145–150

Offenbacher H, Fazekas F, Schmidt R *et al* 1993 Assessment of MRI criteria for a diagnosis of MS. *Neurology* **43**: 905–909

Offner H, Vainiene M, Gold DP *et al* 1992 Characterization of the immune response to a secondary encephalitogenic epitope of basic protein in Lewis rats. I. T cell receptor peptide regulation of T cell clones expressing cross-reactive Vβ genes. *J Immunol* **149**: 1706–1711

Offner H, Buenafe AC, Vainiene M *et al* 1993 Where, when, and how to detect biased expression of disease-relevant Vβ genes in rats with experimental autoimmune encephalomyelitis. *J Immunol* **151**: 506–517

Ogasawara N 1965 Multiple sclerosis with Rosenthal's fibers. *Acta Neuropathol* **5**: 61–68

Ogata J, Feigin I 1975 Schwann cells and regenerated peripheral myelin in multiple sclerosis: an ultrastructural study. *Neurology* **25**: 713–716

Ogawa G, Mochizuki H, Kanzaki M *et al* 2004 Seasonal variation of multiple sclerosis exacerbations in Japan. *Neurol Sci* **24**: 417–419

Oger J, Vorobeychick G, Al-Fahrim A *et al* 1997 Neutralizing antibodies in Betaseron-treated MS patients and in vitro immune function before treatment. *Neurology* **48**: A80

Oh LY, Larsen PH, Krekoski CA *et al* 1999 Matrix metalloproteinase-9/gelatinase B is required for process outgrowth by oligodendrocytes. *J Neurosci* **19**: 8464–8475

Oh LY, Denninger A, Colvin JS *et al* 2003 Fibroblast growth factor receptor 3 signaling regulates the onset of oligodendrocyte terminal differentiation. *J Neurosci* **23**: 883–894

Oh S, Huang X, Chiang C 2005 Specific requirements of sonic hedgehog signaling during oligodendrocyte development. *Dev Dyn* [eub ahead of print]

Ohashi T, Yamamura T, Inobe J-I *et al* 1995 Analysis of proteolipid lipoprotein (PLP)-specific T cells in multiple sclerosis: identification of PLP 95–116 as an HLA-DR2, w15-associated determinant. *Int Immunol* **7**: 1771–1778

Ohe Y, Ishikawa K, Itoh Z, Tatemoto K 1996 Cultured leptomeningeal cells secrete cerebrospinal fluid proteins. *J Neurochem* **67**: 964–971

Ohgoh M, Hanada T, Smith T *et al* 2002 Altered expression of glutamate transporters in experimental autoimmune encephalomyelitis. *J Neuroimmunol* **125**: 170–178

Ohkoshi N, Komatsu Y, Mizusawa H, Kanazawa I 1998 Primary position upbeat nystagmus increased on downward gaze: clinicopathologic study of a patient with multiple sclerosis. *Neurology* **50**: 551–553

Ohlenbusch A, Wilichowski E, Hanefeld F 1998a Characterisation of the mitochondrial genome in childhood multiple sclerosis. III Optic neuritis and LHON mutations. *Neuropaediatrics* **29**: 175–179

Ohlenbusch A, Wilichowski E, Hanefeld F 1998b Characterisation of the mitochondrial genome in childhood multiple sclerosis. III Multiple sclerosis without optic neuritis and the non-LHON associated genes. *Neuropaediatrics* **29**: 313–319

Ohlenbusch A, Pohl D, Hanefeld F 2002 Myelin oligodendrocyte gene polymorphisms and childhood multiple sclerosis. *Paediatr Res* **52**: 175–179

Oikonen M, Laaksonen M, Laippapa P *et al* 2003 Ambient air quality and occurrence of multiple sclerosis relative risk. *Neuroepidemiology* **22**: 95–99

Ojeda V 1984 Necrotising myelopathy associated with malignancy. *Cancer* **53**: 1115–1123

Oka Y, Kanbayashi T, Mezaki T *et al* 2004 Low CSF hypocretin-1/orexin-A associated with hypersomnia secondary to hypothalamic lesion in a case of multiple sclerosis. *J Neurol* **251**: 855–886

Oken BS, Kishiyama S, Zajdel D *et al* 2004 Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology* **62**: 2058–2064

Okinaka S, Tsubaki T, Kuroiwa Y *et al* 1958 Multiple sclerosis and allied diseases in Japan: clinical characteristics. *Neurology* **8**: 756–763

Oksanen V, Gröngagen-Riska C, Fyhrquist F, Somer H 1985 Systemic manifestations and enzyme studies in sarcoidosis with neurologic involvement. *Acta Med Scand* **218**: 123–127

Oksenberg JR, Gaiser CN, Cavalli-Sforza L, Steinman L 1988 Polymorphic markers of human T cell receptor alpha and beta genes: family studies and comparison of frequencies in healthy individuals and patients with multiple sclerosis and myasthenia gravis. *Hum Immunol* **22**: 111–121

Oksenberg JR, Sherritt M, Begovich AB *et al* 1989 T cell receptor V alpha and C alpha alleles associated with multiple sclerosis and myasthenia gravis. *Proc Natl Acad Sci USA* **86**: 988–992

Oksenberg JR, Panzara MA, Begovich AB *et al* 1993 Selection for T-cell receptor vβ-Dβ-Jβ gene rearrangements with specificity for a myelin basic protein peptide in brain lesions of multiple sclerosis. *Nature* **362**: 68–70

Oksenberg JR, Barcellos LF, Cree BA *et al* 2004 Mapping multiple sclerosis susceptibility to the HLA-DR locus in African Americans. *Am J Hum Genet* **74**: 160–167

Okuda Y, Nakatsuji Y, Fujimura H *et al* 1995 Expression of the inducible isoform of nitric oxide synthase in the central nervous system of mice correlates with the severity of actively induced experimental allergic encephalomyelitis. *J. Neuroimmunol* 62: 103–112

Okuda Y, Sakoda S, Fujimura H, Yanagihara T 1997 Nitric oxide via an inducible isoform of nitric oxide synthase is a possible factor to eliminate inflammatory cells from the central nervous system of mice with experimental allergic encephalomyelitis. *J Neuroimmunol* **73**: 107–116

Olafson RA, Rushton JG, Sayre GP 1966 Trigeminal neuralgia in a patient with multiple sclerosis: an autopsy report. *J Neurosurg* **24**: 755–759

Olafsson E, Benedikz J, Hauser WA 1999 Risk of epilepsy in patients with multiple sclerosis: a population-based study in Iceland. *Epilepsia* **40**: 745–747

Oldberg A, Franzen A, Heinegård D 1986 Cloning and sequence analysis of rat bone sialoprotein (osteopontin) cDNA reveals an Arg-Gly-Asp cell-binding sequence. *Proc Natl Acad Sci USA* **83**: 8819–8823

Oldstone MB, Southern PJ 1993 Trafficking of activated cytotoxic T-lymphocytes into the central nervous system: use of a transgenic model. *J Neuroimmunol* **46**: 25–31

Olek MJ, Hohol MJ, Weiner HL 1996 Methotrexate in the treatment of multiple sclerosis. *Ann Neurol* **39**: 684

Olerup O, Hillert J 1991 HLA class II-associated genetic susceptibility in multiple sclerosis: a critical evaluation. *Tissue Antigens* **38**: 1–15

Olerup O, Wallin J, Carlsson B *et al* 1987 Genomic HLA typing by RFLP analysis, using DR beta and DQ cDNA beta probes reveals normal DR-DQ linkages in patients with multiple sclerosis. *Tissue Antigens* **30**: 135–138

Olerup O, Hillert J, Fredrikson S *et al* 1989 Primarily chronic progressive and relapsing/remitting multiple sclerosis: two immunogenetically distinct disease entities. *Proc Natl Acad Sci USA* **86**: 7113–7117

Olerup O, Hillert J, Fredrikson S 1990 The HLA-D region associated MS susceptibility genes may be located telomeric to the HLA-DP sub-region. *Tissue Antigens* **35**: 37–39

Oleson CV, Sivalingam JJ, O'Neill BJ, Staas WE Jr 2003 Transverse myelitis secondary to coexistent Lyme disease and babesiosis. *J Spinal Cord Med* **26**: 168–171

Oleszak EL, Zaczynska E, Bhattacharjee M *et al* 1998 Inducible nitric oxide synthase and nitrotyrosine are found in monocytes/macrophages and/or astrocytes in acute, but not in chronic, multiple sclerosis. *Clin Diagn Lab Immunol* **5**: 438–445

Olgiati R, Jacquet J, Di Prampero PE 1986 Energy cost of walking and exertional dyspnoea in multiple sclerosis. *Am Rev Respir Dis* **134**: 1005–1010

Olindo S, Guillon B, Helias J *et al* 2002 Decrease in heart ventricular ejection fraction during multiple sclerosis. *Eur J Neurol* **9**: 287–291

Olitsky PK, Yager RH 1949 Experimental disseminated encephalomyelitis in white mice. *J Exp Med* **90**: 213–224

Oliveras De Lariva C, Aragones OJM, Mercadet Sobreques J 1968 Estudio de la esclerosis multiple en Asturias. *Neurologia* **6**: 41–45

Oliveri RL, Sibilia G, Valentino P *et al* 1998 Pulsed methylprednisolone induces a reversible impairment of memory in patients with relapsing–remitting multiple sclerosis. *Acta Neurol Scand* **97**: 366–369

Oliverio PJ, Restrepo L, Mitchell SA *et al* 2000 Reversible tacrolimus-induced neurotoxicity isolated to the brain stem. *Am J Neuroradiol* **21**: 1251–1254

Ollivier CP d'Angers 1824 *De la Moelle Epinière et de ses Maladies*. Paris: Crevot

Ollivier CP d'Angers 1827 *Traité de la Moelle Epinière et de ses Maladies*, 2nd edn. Paris: Crevot

Olsen NK, Hansen AW, Nørby S *et al* 1995 Leber's hereditary optic neuropathy with a disorder indistinguishable from multiple sclerosis in a male harbouring the mitochondrial DNA 11778 mutation. *Acta Neurol Scand* **91**: 326–329

Olsson JE, Moller E, Link H 1976 HLA haplotypes in families with high frequency of multiple sclerosis. *Arch Neurol* **33**: 808–812

Olsson T 1992 Immunology of multiple sclerosis. *Curr Opin Neurol Neurosurg* **5**: 195–202

Olsson T 1994 Role of cytokines in multiple sclerosis and experimental autoimmune encephalomyelitis. *Eur J Neurol* **1**: 7–19

Olsson T, Baig S, Hogeberg B, Link H 1990a Anti-myelin basic protein and anti-myelin antibody-producing cells in multiple sclerosis. *Ann Neurol* **47**: 132–136

Olsson T, Zhi WW, Hojeberg B *et al* 1990b Autoreactive T lymphocytes in multiple sclerosis determined by antigen-induced

secretion of interferon-γ. *J Clin Invest* **86**: 981–985
Olsson Y 1974 Mast cells in plaques of multiple sclerosis. *Acta Neurol Scand* **50**: 611–618
O'Malley PP 1966 Severe mental symptoms in disseminated sclerosis: a neuropathological study. *J Irish Med Assoc* **55**: 115–127
Omari KM, John GR, Sealfon SC, Raine CS 2005 CXC chemokine receptors on human oligodendrocytes: implications for multiple sclerosis. *Brain* **128**: 1003–1015
Ombredane A 1929 *Sur les troubles mentaux de la sclérose en plaques*. Paris: Thèse de Paris
Once Weekly Interferon for MS Study Group (OWIMS) 1999 Evidence of interferon beta-1a dose response in relapsing–remitting MS. *Neurology* **53**: 679–686
Onda A, Hamba M, Yabuki S, Kikuchi S 2002 Exogenous tumor necrosis factor-alpha induces abnormal discharges in rat dorsal horn neurons. *Spine* **27**: 1618–1624
O'Neill BP, Moser HW, Saxena KM 1982 Familial X-linked Addison disease as an expression of adrenoleukodystrophy (ALD): elevated C26 fatty acids in cultured skin fibroblasts. *Neurology* **32**: 543–547
O'Neill BP, Marber JR, Forbes GS, Moser HW 1983 Adrenoleucodystrophy: clinical and computerised tomography features of a childhood variant form. *Neurology* **33**: 1203–1205
Ono T, Zambenedetti MR, Yamasaki K *et al* 1998 Molecular analysis of class I (HLA-A and -B) and HLA class II (HLA-DRB1) genes in Japanese patients with multiple sclerosis (Western type and Asian type). *Tissue Antigens* **52**: 539–542
van Oosten BW, Lai M, Barkhof F *et al* 1996a A phase II trial of anti-CD4 antibodies in the treatment of multiple sclerosis. *Mult Scler* **1**: 339–342
van Oosten BW, Rep MHG, van Lier RAW *et al* 1996b A pilot study investigating the effects of orally administered pentoxifylline on selected immune variables in patients with multiple sclerosis. *J Neuroimmunol* **66**: 49–55
van Oosten BW, Lai M, Hodgkinson S *et al* 1997 Treatment of multiple sclerosios with the monoclonal anti-CD4 antibody cM-T412: results of a randomised, double-blind, placebo-controlled, MR monitored phase II trial. *Neurology* **49**: 351–357
van Ooteghem P, De Hooghe MB, Vlietinck R, Carton H 1994 Prevalence of multiple sclerosis in Flanders, Belgium. *Neuroepidemiology* **13**: 220–225
Opal P, Zoghbi HY 2002 The hereditary ataxias. In: Asbury AK, McKhann GM, McDonald WI *et al* (eds) *Diseases of the Nervous System: Clinical Neuroscience and Therapeutic Principles*, 3rd edn. Cambridge: Cambridge University Press, pp. 1880–1895
Opdenakker G, Van-Damme J 1994 Cytokine-regulated proteases in autoimmune diseases. *Immunol Today* **15**:103–107
Opdenakker G, Nelissen I, Van Damme J 2003 Functional roles and therapeutic targeting of gelatinase B and chemokines in multiple sclerosis (review). *Lancet* **2**: 747–756
Openshaw H, Stuve O, Antel JP *et al* 2000a Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor. *Neurology* **54**: 2147–2150
Openshaw H, Lund BT, Kashyap A *et al* 2000b Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and cyclophosphamide conditioning: report of toxicity and immunological monitoring. *Biol Blood Marrow Transplant* **6**: 563–575
Operskalski EA, Visscher BR, Malgren RM, Detels R 1989 A case control study of multiple sclerosis. *Neurology* **39**: 825–829
Oppel G 1963 Mikroskopische Untersuchungen über die Anzahl und Kaliber der markhaltige Nervenfasern im Fasiculus opticus des Menschen. *Graefes Arch Ophthalmol* **160**: 19–27
Oppenheim C, Galanaud D, Samson Y *et al* 2000 Can diffusion weighted magnetic resonance imaging help differentiate stroke from stroke-like events in MELAS? *J Neurol Neurosurg Psychiatry* **69**: 248–250
Oppenheim H 1894 *Lehrbuch der Nervenkrankheiten*. Berlin: S. Karger
Oppenheim H 1911 *Textbook of Nervous Diseases for Physicians and Students* (translated from the 5th edition by A. Bruce). Edinburgh: A Schulze & Co, pp. 332–350
Oppenheim H 1914 Der Formenreichtum der multiplen Sklerose. *Dtsch Z Nervenheilk* **52**: 169–239
Oppenheim H 1917 Über den facialen Typus der multiplen Sklerose. *Neurol Zentralblatt* **36**: 142–143
Oppenheimer D 1978 The cervical cord in multiple sclerosis. *Neuropathol Appl Neurobiol* **4**: 151–162
Oppenheimer DR 1962 *Observations on the Pathology of Demyelinating Disease*. Thesis, University of Oxford
Oppenheimer S, Hoffbrand BI 1986 Optic neuritis and myelopathy in systemic lupus erythematosus. *Can J Neurol Sci* **13**: 129–132
Optic Neuritis Study Group 1991 The clinical profile of optic neuritis. *Arch Ophthalmol* **109**: 1673–1678
Optic Neuritis Study Group 1997a The 5-year risk of MS after optic neuritis: experience of the Optic Neuritis Treatment Trial. *Neurology* **49**: 1404–1413
Optic Neuritis Study Group 1997b Visual function 5 years after optic neuritis. *Arch Ophthalmol* **115**: 1544–1552
Optic Neuritis Study Group 2003 High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis. *Arch Ophthalmol* **121**: 944–949
Orban T 1955 Beitrag zu dem Augenhinter-grundsveranderungen bei Sklerosis multiplex. *Ophthalmolgica* **30**: 387–396
Ordenstein L 1868 *Sur la paralysie agitante et la sclérose en plaques generalisées*. Paris: Delahaye
Orentas DM, Hayes JE, Dyer KL, Miller RH 1999 Sonic hedgehog signaling is required during the appearance of spinal cord oligodendrocyte precursors. *Development* **126**: 2419–2429
O'Riordan JI, Gallagher HL, Thompson AJ *et al* 1996 Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. *J Neurol Neurosurg Psychiatry* **60**: 382–387
O'Riordan JI, Losseff NA, Phatouros C *et al* 1998a Asymptomatic spinal cord lesions in clinical isolated optic nerve, brain stem and spinal cord syndromes suggestive of demyelination. *J Neurol Neurosurg Psychiatry* **64**: 353–357
O'Riordan JI, Thompson AJ, Kingsley DPE *et al* 1998b The prognostic value of brain MRI in clinically isolated syndromes of the CNS: a 10-year follow-up. *Brain* **121**: 495–503
O'Riordan JI, Gomez-Anson B, Moseley IF, Miller DH 1999 Long term MRI follow-up of patients with post infectious encephalomyelitis: evidence of a monophasic disease. *J Neurol Sci* **167**:132–136
O'Riordan S, Nor AM, Hutchinson M 2002 CADASIL imitating multiple sclerosis: the importance of MRI markers. *Mult Scler* **8**: 430–432
Ormerod IEC, McDonald WI 1984 Multiple sclerosis presenting with progressive visual failure. *J Neurol Neurosurg Psychiatry* **47**: 943–946
Ormerod IEC, Miller DH, McDonald WI *et al* 1987 The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study. *Brain* **110**: 1579–1616
Ormerod IEC, Waddy HM, Kermode AG *et al* 1992 Involvement of the central nervous system in chronic inflammatory demyelinating polyneuropathy: a clinical, electrophysiological and magnetic resonance imaging study. *J Neurol Neurosurg Psychiatry* **53**: 789–793
Ormerod IEC, Harding AE, Miller DH *et al* 1994 Magnetic resonance imaging in degenerative ataxic disorders. *J Neurol Neurosurg Psychiatry* **57**: 51–57
Oro AS, Guarino TJ, Driver R *et al* 1996 Regulation of disease susceptibility: decreased prevalence of IgE-mediated allergic disease in patients with multiple sclerosis. *J Allergy Clin Immunol* **97**: 1402–1408
Orr D, McKendrick MM, Sharrack B 2004 Acute disseminated encephalomyelitis temporally associated with campylobacter gastroenteritis. *J Neurol Neurosurg Psychiatry* **75**: 792–793
Ortiz-Ortiz L, Weigle WO 1976 Cellular events in the induction of experimental allergic encephalomyelitis in rats. *J Exp Med* **144**: 604–616
Oski J, Kalimo H, Marttlila RJ *et al* 1996 Inflammatory brain changes in Lyme borreliosis: a report on three patients and review of the literature. *Brain* **119**: 2143–2154
Osler W 1880 Cases of insular sclerosis. *Can Med Surg J* **9**: 1–11
Osler W 1929 *Bibliotecha Osleriana*. A catalogue of books illustrating the history of

medicine and science collected, arranged, and annotated by Sir William Osler, Bt and bequeathed to McGill University. Oxford: Clarendon Press, pp. 675–676

Osoegawa M, Niino M, Ochi H *et al* 2004 Platelet-activating factor acetylhydrolase gene polymorphism and its activity in Japanese patients with multiple sclerosis. *J Neuroimmunol* **150**: 150–156

Osoegawa M, Miyagishi R, Ochi H *et al* 2005 Platelet-activating factor receptor gene polymorphism in Japanese patients with multiple sclerosis. *J Neuroimmunol* **161**: 195–198

Osterhout DJ, Marin-Husstege M, Abano P, Casaccia-Bonnefil P 2002 Molecular mechanisms of enhanced susceptibility to apoptosis in differentiating oligodendrocytes. *J Neurosci Res* **69**: 24–29

Osterman PO 1976 Paroxysmal itching in multiple sclerosis. *Br J Dermatol* **95**: 555–558

O'Sullivan M, Jarosz JM, Martin RJ *et al* 2001 MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. *Neurology* **56**: 628–634

Osuntokun BO 1973 Neurological disorders in Nigeria. In: Spillane JD (ed.) *Tropical Neurology*. London: Oxford University Press, pp. 161–190

Ota K, Matsui M, Milford EL *et al* 1990 T-cell recognition of an immunodominant myelin basic protein epitope in multiple sclerosis. *Nature* **346**: 183–187

Otaegui D, Saenz A, Martinez-Zabaleta M *et al* 2004 Mitochondrial haplogroups in Basque multiple sclerosis patients. *Mult Scler* **10**: 532–535

Ott M, Demisch L, Engelhardt W, Fischer PA 1993 Interleukin-2, soluble interleukin-2-receptor, neopterin, L-tryptophan and beta 2-microglobulin levels in CSF and serum of patients with relapsing–remitting or chronic–progressive multiple sclerosis. *J Neurol* **241**: 108–114

Oturai AB, Larsen F, Ryder LP *et al* 1999 Linkage and association analysis of susceptibility regions on chromosomes 5 and 6 in 106 Scandinavian sibling pair families with multiple sclerosis. *Ann Neurol* **46**: 612–616

Oturai AB, Ryder LP, Fredrikson S *et al* 2004 Concordance for disease course and age of onset in Scandinavian multiple sclerosis coaffected sib pairs. *Mult Scler* **10**: 5–8

Ouardouz M, Nikolaeva MA, Coderre E *et al* 2003 Depolarization-induced Ca2+ release in ischemic spinal cord white matter involves L-type Ca2+ channel activation of ryanodine receptors. *Neuron* **40**: 53–63

Owen JJT, Jenkinson EJ 1984 Early events in T lymphocyte genesis in the fetal thymus. *Am J Anat* **170**: 301–310

Owens GP, Kraus H, Burgoon MP *et al* 1998 Restricted use of V_H4 germline segments in an acute multiple sclerosis brain. *Ann Neurol* **43**: 236–243

Owens GP, Burgoon MP, Anthony J *et al* 2001 The immunoglobulin G heavy chain repertoire in multiple sclerosis plaques is distinct from the heavy chain repertoire in peripheral blood lymphocytes. *Clin Immunol* **98**: 258–263

Owens T 2003 The enigma of multiple sclerosis: inflammation and neurodegeneration causes heterogenous dysfunction and damage. *Curr Opin Neurol* **16**: 259–265

Owens T, Renno T, Taupin V, Krakowski M 1994 Inflammatory cytokines in the brain: does the CNS shape immune responses? *Immunol Today* 15: 566–571

Owens T, Wekerle H, Antel J 2001 Genetic models of CNS inflammation. *Nature Med* **7**: 161–165

Ozawa K, Suchanek G, Breitschopf H *et al* 1994 Patterns of oligodendroglia pathology in multiple sclerosis. *Brain* **117**: 1311–1322

Ozenci V, Kouwenhoven M, Teleshova N *et al* 2000 Multiple sclerosis: pro- and anti-inflammatory cytokines and metalloproteinases are affected differentially by treatment with IFN-beta. *J Neuroimmunol* **108**: 236–243

Ozturk V, Idiman E, Sengun IS, Yulsel Z 2002 Multiple sclerosis and parkinsonism: a report. *Funct Neurol* **17**: 145–147

Pachner AR 2003 Anti-IFNβ antibodies in IFNβ-treated MS patients: summary. *Neurology* **61**: S1–S5

Pachner AR, Steere AC 1985 The triad of neurologic manifestations of Lyme disease: meningitis, cranial neuritis and radiculoneuritis. *Neurology* **35**: 47–53

Pachner AR, Duray P, Steere AC 1989 Central nervous system manifestations of Lyme disease. *Arch Neurol* **46**: 790–795

Padberg F, Haase CG, Feneberg W *et al* 2001 No association between anti-myelin oligodendrocyte glycoprotein antibodies and serum/cerebrospinal fluid levels of the soluble interleukin-6 receptor complex in multiple sclerosis. *Neurosci Lett* **305**: 13–16

Padmashri R, Chakrabarti KS, Sahal D *et al* 2004 Functional characterization of the pentapeptide QYNAD on rNav1.2 channels and its NMR structure. *Pflugers Arch* **447:** 895–907

Padovan E, Casorati G, Dellabona P *et al* 1993 Expression of two T cell receptor alpha chains: dual receptor T cells. *Science* **262**: 422–424

Padovan E, Giachino C, Cella M, Valitutti S, Acuto O, Lanzavecchia A 1995 Normal T lymphocytes can express two different T cell receptor beta chains: implications for the mechanism of allelic exclusion. *J Exp Med* **181**: 1587–1591

Page SA, Verhoef MJ, Stebbins RA *et al* 2003 Cannabis use as described by people with multiple sclerosis. *Can J Neurol Sci* **30**: 201–205

Page WF, Kurtzke JF, Murphy FM, Norman JE 1993 Epidemiology of multiple sclerosis in US veterans: V. Ancestry and the risk of multiple sclerosis. *Ann Neurol* **33**: 632–639

Page WF, Mack TM, Kurtzke JF, Murphy FM, Norman JE 1995 Epidemiology of multiple sclerosis in US veterans: 6. Population ancestry and surname ethnicity as risk factors for multiple sclerosis. *Neuroepidemiology* **14**: 286–296

Paintal AS 1966 The influence of diameter of medullated nerve fibres of cats on the rising and falling phases of the spike and its recovery. *J Physiol* **184**: 791–811

Palace J, Rothwell P 1997 New treatments and azathioprine in multiple sclerosis. *Lancet* **350**: 261

Palacio LG, Rivera D, Builes JJ *et al* 2002 Multiple sclerosis in the tropics: genetic association to STR's loci spanning the HLA and TNF. *Mult Scler* **8**: 249–255

Palffy G 1982 MS in Hungary, including the Gypsy population. In: Kuroiwa Y, Kurland LT (eds) *Multiple Sclerosis: East and West*. Kyushu: Kyushu University Press, pp. 149–157

Palffy G, Merei FT 1961 The possible role of vaccines and sera in the pathogenesis of multiple sclerosis. *World Neurol* **2**: 167–172

Palffy G, Czopf J, Kuntar L, Gyodi E 1994 Multiple sclerosis in Baranya County in Hungarians and in Gypsies. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 274–278

Pambakian AL, Kennard C 1997 Can visual function be restored in patients with homonymous hemianopia? *Br J Ophthalmol* **81**: 324–328

Pamir MN, Kansu T, Erbengi A, Zileli T 1981 Papilloedema in Behçet syndrome. *Arch Neurol* **38**: 643–645

Pandey JP, Goust JM, Salier JP 1981 Immunoglobulin G heavy chain (Gm) allotypes in multiple sclerosis. *J Clin Invest* **67**: 1797–1800

Panelius M 1969 Studies on epidemiological, clinical and etiological aspects of multiple sclerosis. *Acta Neurol Scand* **45 (Suppl 39)**: 1–82

Pang Y, Cai Z, Rhodes PG 2005 Effect of tumor necrosis factor-alpha on developing optic nerve oligodendrocytes in culture. *J Neurosci Res* **80**: 226–234

Panitch HS 1987 Systemic α-interferon in multiple sclerosis. *Arch Neurol* **44**: 61–63

Panitch HS 1994 Influence of infection on exacerbations of multiple sclerosis. *Ann Neurol* **36 (Suppl.)**: S25–S28

Panitch HS, Hirsch RI, Schindler J, Johnson KP 1987a Treatment of multiple sclerosis with gamma-interferon: exacerbation associated with activation of the immune system. *Neurology* **37**: 1097–1102

Panitch HS, Hirsch RL, Haley AS, Johnson KP 1987b Exacerbations of multiple sclerosis in patients treated with gamma interferon. *Lancet* **i**: 893–895

Panitch HS, Bever T, Katz E, Johnson KP 1991 Upper respiratory tract infections trigger attacks of multiple sclerosis in patients treated with interferon. *J Neuroimmunol* **(Suppl 1)**: 125

Panitch HS, Goodin DS, Francis G *et al* 2002 Randomized, comparative study of

interferon beta-1a treatment regimens in MS: the EVIDENCE Trial. *Neurology* **59**: 1496–1506

Pannetier C, Even J, Kourilsky P 1995 T-cell repertoire diversity and clonal expansions in normal and clinical samples. *Immunol Today* **16**: 176–181

Pantano P, Iannetti GD, Caramia F *et al* 2002 Cortical motor reorganization after a single clinical attack of multiple sclerosis. *Brain* **125**: 1607–1615

Paolillo A, Coles AJ, Molyneux PD *et al* 1999 Quantitative MRI in patients with secondary progressive MS treated with monoclonal antibody Campath 1H. *Neurology* **53**: 751–757

Paolillo A, Buzzi MG, Giugni E *et al* 2003 The effect of Bacille Calmette–Guérin on the evolution of new enhancing lesions to hypointense T1 lesions in relapsing remitting MS. *J Neurol* **250**: 247–248

Papadopoulos CM, Tsai S-Y, Alsbiei T *et al* 2002 Functional recovery and neuroanatomical plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat. *Ann Neurol* **51**: 433–441

Papadopoulos V, Micheli A, Nikiforidis D, Mimidis K 2005 Primary biliary cirrhosis complicated by transverse myelitis in a patient without Sjogren's syndrome. *J Postgrad Med* **51**: 43–44

Papais-Alvarenga RM, Miranda-Santos CM, Puccioni-Sohler M *et al* 2002 Optic neuromyelitis syndrome in Brazilian patients. *J Neurol Neurosurg Psychiatry* **73**: 429–435

Papiha SS, Duggan KM, Roberts DF 1991 Factor B (Bf) allotypes and multiple sclerosis in north east England. *Hum Heredity* **41**: 397–402

Parinaud H 1884 Troubles oculaires de la sclérose en plaques. *J Santé Publique* **3**: 3–5

Parisi A, Filice G 2001 Transverse myelitis associated with *Mycoplasma pneumoniae* pneumonitis: a report of two cases. *Infez Med* **9**: 39–42

Parisi, V, Manni G, Spadaro M *et al* 1999 Correlation between morphological and functional retinal impairment in multiple sclerosis patients. *Invest Ophthalmol Vis Sci* **40**: 2520–2527

Park CS 1966 Multiple sclerosis in Korea. *Neurology* **16**: 919–926

Park HJ, Won CK, Pyun KH, Shin HC 1995 Interleukin 2 suppresses afferent sensory transmission in the primary somatosensory cortex. *NeuroReport* **6**: 1018–1020

Park RM 2002 Letter to the editor. *Arch Environ Health* **57**: 383

Park S-K, Miller R, Krane I, Vartanian T 2001a The erbB2 gene is required for the development of terminally differentiated spinal cord oligodendrocytes. *J Cell Biol* **154**: 1245–1258

Park S-K, Solomon D, Vartanian T 2001b Growth factor control of CNS myelination. *Dev Neurosci* **23**: 327–337

Parker GJ, Wheeler-Kingshott CA, Barker GJ 2002 Estimating distributed anatomical brain connectivity using fast marching methods and diffusion tensor imaging. *IEEE Trans Med Imaging* **21**: 505–512

Parker HL 1928 Trigeminal neuralgic pain associated with multiple sclerosis. *Brain* **51**: 46–62

Parker HL 1946 Periodic ataxia. *Collected Papers Mayo Clin* **38**: 642–645

Parkin PJ, Hierons R, McDonald WI 1984 Bilateral optic neuritis: a long-term follow up. *Brain* **107**: 951–964

Parmley VC, Schiffman JS, Maitland CG, Miller NR, Dreyer RF, Hoyt WF 1987 Does neuroretinitis rule out multiple sclerosis? *Arch Neurol* **44**: 1045–1048

Parry AM, Corkill R, Blamire AM *et al* 2003a Beta-interferon does not always slow the progression of axonal injury in multiple sclerosis. *J Neurol* **250**: 171–178

Parry AM, Scott RB, Palace J *et al* 2003b Potentially adaptive functional changes in cognitive processing for patients with multiple sclerosis and their acute modulation by rivastigmine. *Brain* **126**: 2750–2760

Pasare C, Medzhitov R 2003 Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. *Science* **299**: 1033–1036

Pascual-Leone A, Altafullah I, Dhuna A 1991 Hemiageusia: an unusual presentation of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **54**: 657

Pashenkov M, Huang YM, Kostulas V *et al* 2001 Two subsets of dendritic cells are present in human cerebrospinal fluid. *Brain* **124**: 480–492

Pashenkov M, Söderström M, Link H 2003a Secondary lymphoid organ chemokines are elevated in the cerebrospinal fluid during central nervous system inflammation. *J Neuroimmunol* **135**: 154–160

Pashenkov M, Teleshova N, Link H 2003b Inflammation in the central nervous system: the role for dendritic cells. *Brain Pathol* **13**: 23–33

Pasternak JF, De Vivo DC, Prensky AL 1980 Steroid-responsive encephalomyelitis in childhood. *Neurology* **30**: 481–486

Patarca R, Freeman GJ, Singh RR *et al* 1989 Structural and functional studies of the early T lymphocyte activation 1 (*ETA1*) gene: definition of a novel T cell dependent response associated with genetic resistance to bacterial infection. *J Exp Med* **170**: 145–161

Paterson PY 1960 Transfer of allergic encephalomyelitis in rats by means of lymph node cells. *J Exp Med* **111**: 119–135

Pathak R, Khare KC 1967 Disseminated sclerosis syndrome following antirabic vaccination. *J Indian Med Assoc* **49**: 484–485

Patten SB, Metz LM, and Group SS 2002 Interferon beta1a and depression in secondary progressive MS: data from the SPECTRIMS Trial. *Neurology* **59**: 744–746

Patten SB, Beck CA, Williams JV *et al* 2003 Major depression in multiple sclerosis: a population-based perspective. *Neurology* **61**: 1524–1527

Patterson DL, Yunginger JW, Dunn WF *et al* 1995 Anaphylaxis induced by the carboxymethylcellulose component of injectable triamcinolone acetonide suspension (Kenalog). *Ann Allergy Asthma Immunol* **74**: 163–166

Patterson VH, Heron JR 1980 Visual field abnormalities in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **43**: 205–208

Patti F, Cataldi ML, Nicoletti F *et al* 2001 Combination of cyclophosphamide and interferon-beta halts progression in patients with rapidly transitional multiple sclerosis. *J Neurol Neurosurg Psychiatry* **71**: 404–407

Patti F, Ciancio MR, Reggio E *et al* 2002 The impact of outpatient rehabilitation on quality of life in multiple sclerosis. *J Neurol* **249**: 1027–1033

Paty DW, Ebers GC 1998 *Multiple Sclerosis*. Philadelphia: F.A. Davis

Paty DW, Poser C 1984 *The Diagnosis of Multiple Sclerosis*. New York: Thieme-Stratton

Paty DW, Cousin HK, Read S, Adlakha K 1978 Linoleic acid in multiple sclerosis: failure to show any therapeutic benefit. *Acta Neurol Scand* **58**: 53–58

Paty DW, Blume WT, Brown WF, Jaatoul N, Kertesz A, McInnis W 1979 Chronic progressive myelopathy: investigation with CSF electrophoresis, evoked potentials and CT scan. *Ann Neurol* **6**: 419–424

Paty DW, Oger JJ, Kastrukoff LF *et al* 1988 MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding and CT. *Neurology* **38**: 180–185

Paty DW, Li DKB, The IFNB Multiple Sclerosis Study Group 1993 Interferon beta-1b is effective in relapsing–remitting multiple sclerosis: MRI results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* **43**: 662–667

Paty DW, Studney D, Redekop K, Lublin F 1994 MS COSTAR: a computerised patient record adapted for clinical research purposes. *Ann Neurol* **36 (Suppl)**: S134–S135

Paty DW, Arnason B, Li D, Traboulsee A 2003 Interferons in relapsing remitting multiple sclerosis. *Lancet* **361**: 1822; author reply 1823–1824.

Patzold T, Schwengelbeck M, Ossege LM *et al* 2002 Changes of the MS functional composite and EDSS during and after treatment of relapses with methylprednisolone in patients with multiple sclerosis. *Acta Neurol Scand* **105**: 164–168

Patzold U, Pocklington PR 1982 Course of multiple sclerosis: first results of a prospective study carried out of 102 MS patients from 1976–1980. *Acta Neurol Scand* **65**: 248–266

Patzold U, Hecker H, Pocklington P 1982 Azathioprine in treatment of multiple sclerosis. *J Neurol Sci* **54**: 377–394

Pavelko KD, van Engelen BGM, Rodriguez M 1998 Acceleration in the rate of CNS remyelination in lysolecithin-induced demyelination. *J Neurosci* **18**: 2498–2505

Payami H, Thomson G, Motro U, Louis E, Hudes E 1985 The affected sib method IV. Sib trios. *Ann Hum Genet* **49**: 303–314

Pazmany T, Kosa JP, Tomasi TB *et al* 2000 Effect of transforming growth factor-β_1 on microglial MHC-class II expression. *J Neuroimmunol* **103**: 122–130

Peces R, Urra JM, Escalada P *et al* 1993 High dose of methyl-prednisolone inhibits the OKT3-induced cytokine related syndrome (letter). *Nephron* **63**: 118

Pedersen L, Trojaborg W 1981 Visual, auditory and somatosensory pathway involvement in hereditary cerebellar ataxia, Friedreich's ataxia and familial spastic paraplegia. *Electroencephalogr Clin Neurophysiol* **52**: 283–297

Pedersen RA, Troost BT, Abel LA, Zorub D 1980 Intermittent downbeat nystagmus and oscillopsia reversed by suboccipital craniectomy. *Neurology* **30**: 1239–1242

Pedotti R, Mitchell D, Wedemeyer J *et al* 2001 An unexpected version of horror autotoxicus: anaphylactic shock to a self peptide. *Nature Med* **2**: 216–222

Pehl U, Schmid HA 1997 Electrophysiological response of neurons in the rat spinal cord to nitric oxide. *Neuroscience* **77**: 563–573

Pekmezovic T, Jarebinski M, Drulovic J *et al* 2001 Prevalence of multiple sclerosis in Belgrade, Yugoslavia. *Acta Neurol Scand* **104**: 353–357

Pekmezovic T, Jarebinski M, Drulovic J *et al* 2002 Survival of multiple sclerosis patients in the Belgrade population. *Neuroepidemiology* **21**: 235–240

Pekny M, Leveen P, Pekna M *et al* 1995 Mice lacking glial fibrillary acidic protein display astrocytes devoid of intermediate filaments but develop and reproduce normally. *EMBO J* **14**: 1590–1598

Pelanda R, Schwers S, Sonoda E *et al* 1997 Receptor editing in a transgenic mouse model: site, efficiency, and role in cell tolerance and antibody diversification. *Immunity* **7**: 765–775

Peles E, Salzer JL 2000 Molecular domains of myelinated axons. *Curr Opin Neurobiol* **10**: 558–565

Peletier D, Nelson SJ, Oh J *et al* 2003 MRI lesion volume heterogeneity in primary progressive MS in relation with axonal damage and brain atrophy. *J Neurol Neurosurg Psychiatry* **74**: 950–952

Pelletier J, Habib M, Brouchon M *et al* 1992 Etude du transfert interhémisphérique dans la sclérose en plaques. Corrélations morpho-fonctionelles. *Rev Neurol* **148**: 672–679

Pelosi L, Geesken JM, Holly M *et al* 1997 Working memory impairment in early multiple sclerosis: evidence from an event-related potential study of patients with clinically isolated myelopathy. *Brain* **120**: 2039–2058

Pena-Rossi C, McAllister A, Fiette L, Brahic M 1991 Theiler's virus infection induces a specific cytotoxic T lymphocytic response. *Cell Immunol* **138**: 341–348

Pencek TL, Schauf CL, Low PA *et al* 1980 Disruption of the perineurium in amphibian peripheral nerve: morphology and physiology. *Neurology* **30**: 593–599

Pender MP 1988a The pathophysiology of myelin basic protein-induced acute experimental allergic encephalomyelitis in the Lewis rat. *J Neurol Sci* **86**: 277–289

Pender MP 1988b The pathophysiology of acute experimental allergic encephaolmyelitis induced by whole spinal cord in the Lewis rat. *J Neurol Sci* **84**: 209–222

Pender MP 1989 Recovery from acute experimental allergic encephalomyelitis in the Lewis rat: early restoration of nerve conduction and repair by Schwann cells and oligodendrocytes. *Brain* **112**: 393–416

Pender MP 1998 Genetically determined failure of activation-induced apoptosis of autoreactive T cells as a cause of multiple sclerosis. *Lancet* **351**: 978–981

Pender MP 1999 Activation-induced apoptosis of autoreactive and alloreactive T lymphocytes in the target organ as a major mechanism of tolerance. *Immunol Cell Biol* **77**: 216–223

Pender MP, Chalk JB 1989 Connective tissue disease mimicking multiple sclerosis. *Aust NZ J Med* **19**: 469–472

Pender MP, Sears TA 1984 The pathophysiology of acute experimental allergic encephalo-myelitis in the rabbit. *Brain* **107**: 699–726

Pender MP, Nguyen KB, McCombe PA, Kerr JFR 1991 Apoptosis in the nervous system in experimental allergic encephalomyelitis. *J Neurol Sci* **104**: 81–87

Penderis J, Shields SA, Franklin RJ 2003a Impaired remyelination and depletion of oligodendrocyte progenitors does not occur following repeated episodes of focal demyelination in the rat central nervous system. *Brain* **126**: 1382–1391

Penderis J, Woodruff RH, Lakatos A *et al* 2003b Increasing local levels of neuregulin (glial growth factor-2) by direct infusion into areas of demyelination does not alter remyelination in the rat CNS. *Eur J Neurosci* **18**: 2253–2264

Penfield W 1924 Oligodendroglia and its relation to classical neuroglia. *Brain* **47**: 430–452

Penfield W 1932 Neuroglia, normal and pathological. In: Penfield W, Paul B (eds) *Cytology and Cellular Pathology of the Nervous System*. New York: Hoeber, pp. 421–481

Penn RD, Kroin JS 1985 Continuous intrathecal baclofen for severe spasticity. *Lancet* **ii**: 125–127

Penn RD, Savoy SM, Corcos D *et al* 1989 Intrathecal baclofen for severe spinal spasticity. *N Engl J Med* **320**: 1517–1521

Pennypacker KR, Hong J-S, Mullis SB *et al* 1996 Transcription factors in primary glial cultures: changes with neuronal interactions. *Mol Brain Res* **37**: 224–230

Penrose LS 1935 The detection of autosomal linkage in data which consists of pairs of brothers and sisters of unspecified parentage. *Ann Eugen* **6**: 133–138

Pentland B, Ewing DJ 1987 Cardiovascular reflexes in multiple sclerosis. *Eur Neurol* **26**: 46–50

Pépin B, Goldstein B, Man HX *et al* 1978 Maldie de Eales avec manifestations neurologiques. *Rev Neurol* **134**: 427–436

Percy AK, Nobrega FT, Ozaki H *et al* 1971 Multiple sclerosis in Rochester, Minnesota: a 60-year appraisal. *Arch Neurol* **25**: 105–111

Percy AK, Nobrega FT, Kurland LT 1972 Optic neuritis and multiple sclerosis. *Arch Ophthalmol* **87**: 135–139

Peress NS, Perillo E, Seidman RJ 1996 Glial transforming growth factor (TGF)-β isotypes in multiple sclerosis: differential expression of TGF-β1, 2 and 3 isotypes in multiple sclerosis. *J Neuroimmunol* **71**: 115–123

Perez L, Alvarez-Cermeno JC, Rodriguez C *et al* 1995 B cells capable of spontaneous IgG secretion in cerebrospinal fluid from patients with multiple sclerosis: dependency on local IL-6 production. *Clin Exp Immunol* **101**: 449–452

Pericak-Vance MA, Rimmler JB, Martin ER *et al* 2001 Linkage and association analysis of chromosome 19q13 in multiple sclerosis. *Neurogenetics* **3**: 195–201

Pericak-Vance MA, Rimmler JB, Haines JL *et al* 2004 Investigation of seven proposed regions of linkage in multiple sclerosis: an American and French collaborative study. *Neurogenetics* **5**: 45–48

Pericot I, Brieva L, Tintore M *et al* 2003 Myelopathy in seronegative Sjogren syndrome and/or primary progressive multiple sclerosis. *Mult Scler* **9**: 256–259

Perier O, Gregoire A 1965 Electron microscopic features of multiple sclerosis. *Brain* **88**: 937–952

Perini P, Gallo P 2001 The range of multiple sclerosis associated with neurofibromatosis type 1. *J Neurol Neurosurg Psychiatry* **71**: 679–681

Perini P, Tagliaferri C, Belloni M *et al* 2001 The HLA-DR13 haplotype is associated with 'benign' multiple sclerosis in northeast Italy. *Neurology* **57**: 158–159

Perkin GD, Rose FC 1979 *Optic Neuritis and its Differential Diagnosis*. Oxford: Oxford University Press

Perks WH, Lascelles RG 1976 Paroxysmal brain stem dysfunction as presenting feature of multiple sclerosis. *Br Med J* **2**: 1175–1176

Perlin MW, Lancia G, Ng SK 1995 Toward fully automated genotyping: genotyping microsatellite markers by deconvolution. *Am J Hum Genet* **57**: 1199–1210

Perrin PJ, Maldonado JH, Davis TA *et al* 1996 CTLA-4 blockade enhances clinical disease and cytokine production during experimental allergic encephalomyelitis. *J Immunol* **157**: 1333–1336

Perron H, Geny C, Laurent A *et al* 1989 Leptomeningeal cell line from multiple sclerosis with reverse transcriptase activity and viral particles. *Res Virol* **140**: 551–561

Perron H, Lalande B, Gratacap B *et al* 1991 Isolation of retrovirus from patients with multiple sclerosis. *Lancet* **337**: 862–863

Perron H, Gratacap B, Lalande B *et al* 1992 *In vitro* transmission and antigenicity of a retrovirus isolated from a multiple sclerosis patient. *Res Virol* **143**: 337–350

Perron H, Garson JA, Bedin F *et al* 1997 Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. The Collaborative Research Group on Multiple Sclerosis. *Proc Natl Acad Sci USA* **94**: 7583–7588

Perron H, Jouvin-Marche E, Michel M *et al* 2001 Multiple sclerosis retrovirus particles and recombinant envelope trigger an abnormal immune response in vitro, by inducing polyclonal Vβ16 T-lymphocyte activation. *Virology* **287**: 321–332

Perron H, Lazarini F, Ruprecht K *et al* 2005 Human endogenous retrovirus (HERV)-W ENV and GAG proteins: physiological expression in human brain and pathological modulation in multiple sclerosis lesions. *J Neurovirol* **11**: 22–33

Perry LL, Barzaga-Gilbert E, Trotter JL 1991 T cell sensitization to proteolipid protein in myelin basic protein-induced relapsing experimental allergic encephalomyelitis. *J Neuroimmunol* **33**: 7–15

Perry VH 1998 A revised view of the central nervous system microenvironment and major histocompatibility complex class II antigen presentation. *J Neuroimmunol* **90**: 113–121

Perry VH, Tsao JW, Feam S, Brown MC 1995 Inflammation in the nervous system. *Curr Opin Neurobiol* **5**: 636–641

Persson HE, Sachs C 1981 Visual evoked potentials elicited by pattern reversal during provoked visual impairment in multiple sclerosis. *Brain* **104**: 369–382

Pertschuk LP, Cook AW, Gupta J 1976 Measles antigen in multiple sclerosis: identification in the jejunum by immunofluorescence. *Life Sci* **19**: 1603–1608

Peselow ED, Fieve RR, Deutsch SI, Kaufman M 1981 Coexistent manic symptoms and multiple sclerosis. *Psychosomatics* **22**: 824–825

Petajan JH, White AT 2000 Motor-evoked potentials in response to fatiguing grip exercise in multiple sclerosis patients. *Clin Neurophysiol* **111**: 2188–2195

Petajan JH, Gappmaier E, White AT *et al* 1996 Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* **39**: 432–441

Peter JB, Boctor FN, Tourtellottee WW 1991 Serum and CSF levels of IL-2, sIL-2R, TNF-alpha, and IL-1-beta: expected lack of clinical utility. *Neurology* **41**: 121–123

Petereit HF, Bamborschke S, Esse AD, Heiss WD 1997 Interferon gamma producing blood lymphocytes are decreased by interferon beta therapy in patients with multiple sclerosis. *Mult Scler* **3**: 180–183

Petereit HF, Lindemann H, Schoppe S 2003 Effect of immunomodulatory drugs on in vitro production of brain-derived neurotrophic factor. *Mult Scler* **9**: 16–20

Peters A, Proskauer CC 1969 The ratio between myelin segments and oligodendrocytes in the optic nerve of adult rats. *Anat Rec* **163**: 243–251

Peters A, Palay SL, Webster HF 1976 *The Fine Structure of the Nervous System: The Neurones and Supporting Cells*. Philadephia: W.B. Saunders

Peters GB, Bakri SJ, Krohel GB 2002 Cause and prognosis of nontraumatic sixth nerve palsies in young adults. *Ophthalmology* **109**: 1925–1928

Petersen P, Kastrup J, Zeeberg I, Boysen G 1986 Chronic pain treatment with intravenous lidocaine. *Neurol Res* **8**: 189–190

Peterson JW, Bo L, Mork S *et al* 2001 Transsected neurites, apoptotic neurons and reduced inflammation in cortical multiple sclerosis lesions. *Ann Neurol* **50**: 389–400

Peterson JW, Bo L, Mork S *et al* 2002 VCAM-1 positive microglia target oligodendrocytes at the border of multiple sclerosis lesions. *J Neuropathol Exp Neurol* **61**: 539–546

Petito CK, Navia BA, Cho E-S, Jordon BD, George DC, Price RW 1986 Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with acquired immunodeficiency syndrome. *N Engl J Med* **312**: 874–879

Petkau AJ 2003 Statistical approaches to assessing the effects of neutralizing antibodies: IFNβ-1b in the pivotal trial of relapsing–remitting multiple sclerosis. *Neurology* **61 (Suppl 5)**: S35–S37

Petkau AJ, White RA, Ebers GC *et al* 2004 Longitudinal analyses of the effects of neutralizing antibodies on interferon beta-1b in relapsing–remitting multiple sclerosis. *Mult Scler* **10**: 126–138

Petrescu A 1994 Epidemiology of multiple sclerosis in Rumania. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuhtturm-Verlag/LTV Press, pp. 287–293

Petro DJ, Ellenberger C 1981 Treatment of human spasticity with delta-9 tetrahydrocannibinol. *J Clin Pharmacol* **21**: 4135–4165

Pette H 1928 Über die Pathogenese der multiplen Sklerose. *Dtsch Z Nervenheilk* **105**: 76–132

Pette M, Fujita K, Kitze B *et al* 1990a Myelin basic protein-specific T lymphocyte lines from MS patients and healthy individuals. *Neurology* **40**: 1770–1776

Pette M, Fujita K, Wilkinson D *et al* 1990b Myelin autoreactivity in multiple sclerosis: recognition of myelin basic protein in the context of HLA-DR2 products by T lymphocytes of multiple sclerosis patients and healthy donors. *Proc Natl Acad Sci USA* **87**: 7968–7972

Pette M, Pette DF, Muraro PA *et al* 1997 Interferon-β interferes with the proliferation but not the cytokine secretion of myelin basic protein-specific, T-helper type 1 lymphocytes. *Neurology* **49**: 385–392

Petty GW, Matteson EL, Younge BR *et al* 2001 Recurrence of Susac syndrome (retinocochleocerebral vasculopathy) after remission of 18 years. *Mayo Clin Proc* **76**: 958–960

Petty MA, Lo EH 2002 Junctional complexes of the blood-brain barrier: permeability changes in neuroinflammation. *Progr Neurobiol* **68**: 311–323

Petzold A, Eikelenboom MJ, Gveric D *et al* 2002 Markers for different glial cell responses in multiple sclerosis: clinical and pathological correlations. *Brain* **125**: 1462–1473

Petzold A, Eikelenboom MJ, Keir GJ *et al* 2005 Axonal damage accumulates in the progressive stage of multiple sclerosis: a 3-year follow up study. *J Neurol Neurosurg Psychiatry* **76**: 206–211

Peyser JM, Edwards JR, Poser CM, Filskov SB 1980 Cognitive function in patients with multiple sclerosis. *Arch Neurol* **37**: 577–579

Peyser JM, Rao SM, LaRocca NG, Kaplan E 1990 Guidelines for neuropsychologic research in multiple sclerosis. *Arch Neurol* **47**: 94–97

Pfausler B, Engelhardt K, Kampfl A *et al* 2002 Post-infectious central and peripheral nervous system diseases complicating *Mycoplasma pneumoniae* infection: report of three cases and review of the literature. *Eur J Neurol* **9**: 93–96

Phadke JG 1987 Survival patterns and cause of death in patients with multiple sclerosis: results from an epidemiological survey in north east Scotland. *J Neurol Neurosurg Psychiatry* **50**: 523–531

Phadke JG 1990 Clinical aspects of multiple sclerosis in north-east Scotland with particular reference to its course and prognosis. *Brain* **113**: 1597–1628

Phadke JG, Best PV 1983 Atypical and clinically silent multiple sclerosis: a report of 12 cases discovered unexpectedly at necropsy. *J Neurol Neurosurg Psychiatry* **46**: 414–420

Phadke JG, Downie AW 1987 Epidemiology of multiple sclerosis in the North East (Grampian Region) of Scotland – an update. *J Epidemiol Commun Hlth* **41**: 5–13

Pham DL, Prince JL 1999 An adaptive fuzzy C-means algorithm for image segmentation in the presence of intensity in homogeneities. *Patt Recog Lett* **20**: 57–68

Pham DL, Xu C, Prince JL 2000 Current methods in medical image segmentation. *Annu Rev Biomed Engl* **2**: 315–337

Pham-Dinh D, Mattei M-G, Nussbaum J-L *et al* 1993 Myelin/oligodendrocyte glycoprotein is a member of a subset of the immunoglobulin superfamily encoded within the major histocompatibility complex. *Proc Natl Acad Sci USA* **90**: 7990–7994

Phokeo V, Ball AK 2000 Transection of dysmyelinated optic nerve axons in adult rats lacking myelin basic protein. *NeuroReport* **11**: 3375–3379

Piani D, Frei K, Do K *et al* 1991 Murine brain macrophages induce NMDA receptor mediated neurotoxicity in vitro by secreting glutamate. *Neurosci Lett* **133**: 159–162

Pichichero ME, Cernichiari E, Lopreiato J, Treanor J 2002 Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet* **360**: 1737–1741

Pickard C, Mann C, Sinnott P *et al* 1999 Interleukin-10 (IL10) promoter polymorphisms and multiple sclerosis. *J Neuroimmunol* **101**: 207–210

Pickett GE, Bisnaire D, Ferguson GG 2005 Percutaneous retrogasserian glycerol rhizotomy in the treatment of tic douloureux associated with multiple sclerosis. *Neurosurgery* **56**: 537–45; discussion 537–545

Pickuth D, Heywang-Kobrunner SH 2000 Neurosarcoidosis: evaluation with MRI. *J Neuroradiol* **27**: 185–188

Piddlesden SJ, Morgan BP 1993 Killing of rat glial cells by complement: deficiency of the rat analogue of CD59 is the cause of oligodendrocyte susceptibility to lysis. *J Neuroimmunol* **48**: 169–176

Piddlesden S, Lassmann H, Laffafian I *et al* 1991 Antibody-mediated demyelination in experimental allergic encephalomyelitis is independent of complement membrane attack complex formation. *Clin Exp Immunol* **83**: 245–250

Piddlesden S, Lassmann H, Zimprich F *et al* 1993 The demyelinating potential of antibodies to myelin oligodendrocyte glycoprotein is related to their ability to fix complement. *Am J Pathol* **143**: 555–564

Piddlesden SJ, Storch MK, Hibbs M *et al* 1994 Soluble recombinant complement receptor 1 inhibits inflammation and demyelination in antibody-mediated demyelinating experimental allergic encephalomyelitis. *J Immunol* **152**: 5477–5484

Pierani A, Brenner-Morton S, Chiang C, Jessell TM 1999 A sonic hedgehog-independent, retinoid-activated pathway of neurogenesis in the ventral spinal cord. *Cell* **97**: 903–915

Pierig R, Belliveau J, Amouri R *et al* 2002 Association of a gliotoxic activity with active multiple sclerosis in US patients. *Cell Mol Biol* **48**: 199–203

Piéron R, Coulaud J M, Debure A *et al* 1979 Nevrite optique et sarcoidose. *Semaine Hôpitaux* **55**: 137–139

Pihlaja H, Rantamaki T, Wikstrom T *et al* 2003 Linkage disequilibrium between the MBP tetranucleotide repeat and multiple sclerosis is restricted to a geographically-defined subpopulation in Finland. *Genes Immun* **4**: 138–146

Pina MA, Ara JR, Modrego PJ *et al* 1998 Prevalence of multiple sclerosis in the sanitary district of Calatayud, Northern Spain: is Spain a zone of high risk for this disease? *Neuroepidemiology* **17**: 258–264

Pina MA, Ara JR, Lasierra P *et al* 1999 Study of HLA as a predisposing factor and its possible influence on the outcome of multiple sclerosis in the sanitary district of Calatayud, northern Spain. *Neuroepidemiology* **18**: 203–209

Pinching A 1977 Clinical testing of olfaction reassessed. *Brain* **100**: 377–388

Piperidou HN, Heliopoulos IN, Maltezos ES, Milonas IA 2003 Epidemiological data of multiple sclerosis in the province of Evros, Greece. *Eur Neurol* **49**: 8–12

Pirttila T, Nurmikko T 1995 CSF oligoclonal bands, MRI, and the diagnosis of multiple sclerosis. *Acta Neurol Scand* **92**: 468–471

Pirttila T, Haanpaa M, Mehta PD, Lehtimaki T 2000 Apolipoprotein E (APOE) phenotype and APOE concentrations in multiple sclerosis and acute herpes zoster. *Acta Neurol Scand* **102**: 94–98

Pitt D, Werner P, Raine CS 2000 Glutamate excitotoxicity in a model of multiple sclerosis. *Nature Med* **6**: 67–70

Pittock SJ, Keir G, Alexander M *et al* 2001 Rapid clinical and CSF response to intravenous gamma globulin in acute disseminated encephalomyelitis. *Eur J Neurol* **8**: 725

Pittock SJ, Mayr WT, McClelland RL *et al* 2004a Change in MS-related disability in a population-based cohort: a 10-year follow-up study. *Neurology* **62**: 51–59

Pittock SJ, Mayr WT, McClelland RL *et al* 2004b Disability profile of MS did not change over 10 years in a population-based prevalence cohort. *Neurology* **62**: 601–606

Pittock SJ, McClelland RL, Mayr WT *et al* 2004c Clinical implications of benign multiple sclerosis: a 20-year population-based follow-up study. *Ann Neurol* **56**: 303–306

Pittock SJ, McClelland RL, Mayr WT *et al* 2004d Prevalence of tremor in multiple sclerosis and associated disability in the Olmsted County population. *Mov Disord* **19**: 1482–1485

Pitzalis C, Sharrack B, Gray IA *et al* 1997 Comparison of the effects of oral versus intravenous methylprednisolone regimens on peripheral blood T lymphocyte adhesion molecule expression, T cell subsets distribution and TNF alpha concentrations in multiple sclerosis. *J Neuroimmunol* **74**: 62–68

Pizzi M, Sarnico I, Boroni F *et al* 2004 Prevention of neuron and oligodendrocyte degeneration by interleukin-6 (IL-6) and IL-6 receptor/IL6 fusion protein in organotypic hippocampal slices. *Mol Cell Neurosci* **25**: 301–311

Plant GT, Kermode AG, du Boulay EPGH, McDonald WI 1989 Spasmodic torticollis due to a midbrain lesion in a case of multiple sclerosis. *Mov Disord* **4**: 359–362

Plant GT, Kermode AG, Turano G *et al* 1992 Symptomatic retrochiasmal lesions in multiple sclerosis: clinical features, visual evoked potentials, and magnetic resonance imaging. *Neurology* **42**: 68–76

Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group 1997 Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain–Barré syndrome. *Lancet* **349**: 225–230

Plata-Salamán CR, ffrench-Mullen JM 1992 Interleukin-1 beta depresses calcium currents in CA1 hippocampal neurons at pathophysiological concentrations. *Brain Res Bull* **29**: 221–223

Plata-Salamán CR, ffrench-Mullen JMH 1993 Interleukin-2 modulates calcium currents in dissociated hippocampal CAI neurons. *NeuroReport* **4**: 579–581

Plata-Salamán CR, Oomura Y, Kai Y 1988 Tumor necrosis factor and interleukin-1beta suppression of food intake by direct action in the central nervous system. *Brain Res* **448**: 106–114

Platz P, Ryder LP, Staub Nielson L *et al* 1975 HL-A and idiopathic optic neuritis. *Lancet* **i**: 520–521

Plohmann AM, Kappos L, Ammann W *et al* 1998 Computer assisted retraining of attentional impairments in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **64**: 455–462

Pluchino S, Quattrini A, Brambilla E *et al* 2003 Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature* **422**: 688–694

Pluchino S, Zanotti L, Rossi B *et al* 2005 Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature* **436**: 266–271

Plumb J, McQuaid S, Mirakhur M, Kirk J 2002 Abnormal endothelial tight junctions in active lesions and normal appearing white matter in multiple sclerosis. *Brain Pathol* **12**: 199–211

Plumb J, Armstrong MA, Duddy M *et al* 2003 CD83-positive dendritic cells are present in occasional perivascular cuffs in multiple sclerosis lesions. *Mult Scler* **9**: 142–147

Poeck K, Markus P 1964 Gibt es eine gutartige Verlaufsform der multiplen Sklerose. *Münchener Med Wochenschr* **106**: 2190–2197

Pohl D, Rostasy K, Gartner J, Hanefeld F 2005 Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a. *Neurology* **64**: 888–890

Poisson M 1984 Sex hormone receptors in human meningiomas. *Clin Neuropharmacol* **7**: 320–324

Polanczyk M, Zamora A, Subramanian S *et al* 2003 The protective effect of 17beta-estradiol on experimental autoimmune encephalomyelitis is mediated through estrogen receptor-alpha. *Am J Pathol* **163**: 1599–1605

Poland GA, Jacobson RM 2004 Prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med* **351**: 2832–2838

Pollock M, Calder C, Allpress S 1977 Peripheral nerve abnormality in multiple sclerosis. *Ann Neurol* **2**: 41–48

Polman CH, Matthaei I, De Groot CJA *et al* 1988 Low-dose cyclosporin A induces relapsing remitting experimental allergic encephalomyelitis in the Lewis rat. *J Neuroimmunol* **17**: 209–216

Polman CH, Bertelsmann FW, de Waal R *et al* 1994a 4-Aminopyridine is superior to

3,4-diaminopyridine in the treatment of patients with multiple sclerosis. *Arch Neurol* **51**: 1136–1139

Polman CH, Bertelsmann FW, van Loenen AC, Koetsier JC 1994b 4-Aminopyridine in the treatment of patients with multiple sclerosis. *Arch Neurol* **51**: 292–296

Polman CH, Kappos L, White R *et al* 2003 Neutralizing antibodies during treatment of secondary progressive MS with interferon beta-1b. *Neurology* **60**: 37–43

Polman C, Barkhof F, Sandberg-Wollheim M *et al* 2005a Treatment with laquinimod reduces development of active MRI lesions in relapsing MS. *Neurology* **64**: 987–991

Polman CH, Wolinsky JS, Reingold SC 2005b Multiple sclerosis diagnostic criteria: three years later. *Mult Scler* **11**: 5–12

Pompidou A, Rancurel G, Delsaux MC *et al* 1986 Clinical and immunological improvement of active multiple sclerosis by isoprinosine treatment: a randomised pilot study. *Presse Med* **15**: 930–931

Pon RA, Freedman MS 2003 Study of Herpesvirus saimiri immortalization of γδ T cells derived from peripheral blood and CSF of multiple sclerosis patients. *J Neuroimmunol* **139**: 119–132

Ponsonby A-L, van der Mei I, Dwyer T *et al* 2005 Exposure to infant siblings during early life and risk of multiple sclerosis. *J Am Med Assoc* **293**: 463–469

Popko B, Corbin JG, Baerwald KD *et al* 1997 The effects of interferon-gamma on the central nervous system. *Mol Neurobiol* **14**: 19–35

Popov VS 1983 Clinical picture and epidemiology of disseminated sclerosis. *Z Nevropatol Psikhiatr Imeni SS Korsakora* **83**: 1330–1334

Popovich PG, Jones TB 2003 Manipulating neuroinflammatory reactions in the injured spinal cord: back to basics. *Trends Pharmacol Sci* **24**: 13–17

Popovic N, Schubart A Goetz BD *et al* 2002 Inhibition of autoimmune encephalomyelitis by a tetracycline. *Ann Neurol* **51**: 215–223

Porrini AM, Gambi D, Reder AT 1995 Interferon effects on interleukin-10 secretion: mononuclear cell response to interleukin-10 is normal in multiple sclerosis patients. *J Neuroimmunol* **61**: 27–34

Porst H 1997 Transurethral alprostadil with MUSE (medicated urethral system for erection) vs intra-cavernous alprostadil: a comparative study in 103 patients with erectile dysfunction. *Int J Impotence Res* **9**: 187–192

Porter B, Keenan E 2003 Nursing at a specialist diagnostic clinic for multiple sclerosis. *Br J Nursing* **12**: 650–656

Porter S 2004 An historical whodunit. *Biologist* **51**: 109–113

Poser CM 1965 Clinical diagnostic criteria in epidemiological studies of multiple sclerosis. *Ann NY Acad Sci* **122**: 506–519

Poser CM 1982 Neurological complications of swine influenza vaccination. *Acta Neurol Scand* **66**: 413–431

Poser CM 1987a The peripheral nervous system in multiple sclerosis: a review and pathogenetic hypothesis. *J Neurol Sci* **79**: 83–90

Poser CM 1987b Trauma and multiple sclerosis: an hypothesis. *J Neurol* **234**: 155–159

Poser CM 1994 The dissemination of multiple sclerosis: a Viking saga? A historical essay. *Ann Neurol* **36 (Suppl 2)**: S231–S243

Poser CM 1995 Viking voyages: the origin of multiple sclerosis? *Acta Neurol Scand* **161 (Suppl)**: 11–22

Poser CM 2000 Trauma to the central nervous system may result in formation or enlargement of multiple sclerosis plaques. *Arch Neurol* **57**: 1074–1076

Poser CM, Brinar VV 2003 Epilepsy and multiple sclerosis. *Epilepsy Behav* **4**: 6–12

Poser CM, Hibberd PL 1988 Analysis of the 'epidemic' of multiple sclerosis in the Faroe Islands. II. Biostatistical aspects. *Neuroepidemiology* **7**: 181–189

Poser CM, Vernant J 1993 La sclérose en plaques dans le race noire. *Bull Soc Pathol Exotique* **86**: 1–5

Poser CM, Presthus J, Hörsdal O 1966 Clinical characteristics of autopsy-proven multiple sclerosis. *Neurology* **16**: 791–798

Poser CM, Paty DW, Scheinberg L *et al* 1983 New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* **13**: 227–231

Poser CM, Hibberd PL, Benedicz J, Gudmundsson G 1988 Analysis of the 'epidemic' of multiple sclerosis in the Faroe Islands. I. Clinical and epidemiological *aspects. Neuroepidemiology* **7**: 168–180

Poser CM, Roman GC, Vernant J-C 1990 Multiple sclerosis or HTLV-1 myelitis. *Neurology* **40**: 1020–1022

Poser CM, Benedikz J, Hibberd PL 1992 The epidemiology of multiple sclerosis: the Iceland model. Onset-adjusted prevalence rate and other methodological considerations. *J Neurol Sci* **111**: 143–152

Poser S 1978 Multiple sclerosis. In: *An Analysis of 812 Cases by Means of Electronic Data Processing*. Berlin: Springer-Verlag

Poser S 1994 The epidemiology of multiple sclerosis in southern Lower Saxony. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press: pp. 130–133

Poser S, Hauptvogel H 1973 Clinical data from 418 MS patients in relation to the diagnosis: first experiences with an optical mark reader documentation system. *Acta Neurol Scand* **49**: 473–479

Poser S, Kurtzke JF 1991 Epidemiology of MS (letter to the editor). *Neurology* **41**: 157–158

Poser S, Poser W 1983 Multiple sclerosis and gestation. *Neurology* **33**: 1422–1427

Poser S, Hermann-Grevels I, Wikstrom J, Poser W 1978 Clinical features of the spinal form of multiple sclerosis. *Acta Neurol Scand* **57**: 151–158

Poser S, Raun NE, Wikstrom J, Poser W 1979a Pregnancy, oral contraceptives and multiple sclerosis. *Acta Neurol Scand* **59**: 108–118

Poser S, Wikström J, Bauer HJ 1979b Clinical data and identification of special forms of multiple sclerosis with a standardised documentation system. *J Neurol Sci* **40**: 159–168

Poser S, Bauer HJ, Poser W 1982a Prognosis of multiple sclerosis: results from an epidemiological area in Germany. *Acta Neurol Scnad* **65**: 347–354

Poser S, Raun NE, Poser W 1982b Age of onset, initial symptomatology and the course of multiple sclerosis. *Acta Neurol Scand* **66**: 355–362

Poser S, Poser W, Schlaf G *et al* 1986 Prognostic indicators in multiple sclerosis. *Acta Neurol Scand* **74**: 387–392

Poser S, Kurtzke JF, Schlaf G 1989a Survival in multiple sclerosis. *J Clin Epidemiol* **42**: 159–168

Poser S, Stickel B, Krtsch U *et al* 1989b Increasing incidence of multiple sclerosis in south Lower Saxony, Germany. *Neuroepidemiology* **8**: 207–213

Poser S, Luer W, Bruhn H *et al* 1992 Acute demyelinating disease: classification and non invasion diagnosis. *Acta Neurol Scand* **86**: 597–585

Poskanzer DC, Schapira K, Miller H 1963 Epidemiology of multiple sclerosis in the counties of Northumberland and Durham. *J Neurol Neurosurg Psychiatry* **26**: 368–376

Poskanzer DC, Walker AM, Yon Kondi J, Sheridan JL 1976 Studies in the epidemiology of multiple sclerosis in the Orkney and Shetland Islands. *Neurology* **26**: 14–17

Poskanzer DC, Prenney LP, Sheridan JL, Yon Kondy J 1980a Multiple sclerosis in the Orkney and Shetland Islands. 1. Epidemiology, clinical factors and methodology. *J Epidemiol Commun Hlth* **34**: 229–239

Poskanzer DC, Terasaki PI, Prenney LP *et al* 1980b Multiple sclerosis in the Orkney and Shetland Islands. III. Histocompatibility determinants. *J Epidemiol Commun Hlth* **34**: 253–257

Posner JB 1986 Paraneoplastic syndromes. In: Asbury AK, McKhann GM, McDonald MI (eds) *Diseases of the Nervous System*. Philadephia: W.B. Saunders, pp. 1105–1120

Potemkowski A, Walczak A, Nocon D *et al* 1994 Epidemiological analysis of multiple sclerosis in the Szczecin Region, north-western part of Poland. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 249–254

Powell T, Sussman JG, Davies-Jones GA 1992 MR imaging in acute multiple sclerosis: ringlike appearance in plaques suggesting the presence of paramagnetic free radicals. *Am J Neuroradiol* **13**: 1544–1546

Powers JM, Liu Y, Moser AB, Moser HW 1992 The inflammatory myelinopathy of adreno-leukodystrophy: cells, effector molecules, and pathogenetic implications. *J Neuropath Exp Neurol* **51**: 630–643

Powers JM, DeCiero DP, Ito M *et al* H 2000 Adrenomyeloneuropathy: a neuropathologic

review featuring its noninflammatory myelopathy. *J Neuropath Exp Neurol* **59**: 89–102

Pozza M, Bettelli C, Aloe L *et al* 2000 Further evidence for a role of nitric oxide in experimental allergic encephalomyelitis: aminoguanidine treatment modifies its clinical evolution. *Brain Res* **855**: 39–46

Pozzilli C, Passafiume D, Bernardi S *et al* 1991 SPECT, MRI and cognitive functions in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **54**: 110–115

Pozzilli C, Bastianello S, Koudriavtseva T *et al* 1996 Magnetic resonance imaging changes with recombinant human interferon-β-1a: a short term study in relapsing–remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* **61**: 251–258

Pozzilli C, Brunetti M, Amicosante AM *et al* 2002 Home based management in multiple sclerosis: results of a randomised controlled trial. *J Neurol Neurosurg Psychiatry* **73**: 250–255

Pozzilli C, Palmisano L, Mainero C *et al* 2004 Relationship between emotional distress in caregivers and health status in persons with multiple sclerosis. *Mult Scler* **10**: 442–446

van Praag H, Schinder AF, Christie BR *et al* 2002 Functonal neurogenesis in the adult hippocampus. *Nature* **415**: 1030–1034

Pradhan S, Mishra VN 2004 A central demyelinating disease with atypical features. *Mult Scler* **10**: 308–315

Pradhan S, Gupta RP, Shashank S, Pandey N 1999 Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *J Neurol Sci* **165**: 56–61

Prange AJA, Lauer K, Poser S *et al* 1986 Epidemiological aspects of multiple sclerosis: a comparative study of four centres in Europe. *Neuroepidemiology* **5**: 71–79

Prasad DV, Nguyen T, Li Z *et al* 2004 Murine B7-H3 is a negative regulator of T cells. *J Immunol* **173**: 2500–2506

Prasad RS, Smith SJ, Wright H 2003 Lower abdominal pressure versus external bladder stimulation to aid bladder emptying in multiple sclerosis: a randomized controlled study. *Clin Rehab* **17**: 42–47

Prat A, Al-Asmi A, Duquette P, Antel JP 1999 Lymphocyte migration and multiple sclerosis: relation with disease course and therapy. *Ann Neurol* **46**: 253–256

Pratt RTC 1951 An investigation of the psychiatric aspects of disseminated sclerosis. *J Neurol Neurosurg Psychiatry* **14**: 326–336

Pratt RTC, Compston ND, McAlpine D 1951 The familial incidence of multiple sclerosis and its significance. *Brain* **74**: 191–232

Prelog K, Blome S, Dennis C 2003 Neurosarcoidosis of the conus medullaris and cauda equina. *Australas Radiol* **47**: 295–297

Preston SD, Steart PV, Wilkinson A *et al* 2003 Capillary and arterial cerebral amyloid angiopathy in Alzheimer's disease: defining the perivascular route for the elimination of amyloid beta from the human brain. *Neuropathol Appl Neurobiol* **29**: 106–117

Previdi P, Buzzi P 1992 Paroxysmal dystonia due to a lesion of the cervical cord: case report. *Ital J Neurosci* **13**: 521–523

Pribyl TM, Campagnoni CW, Kampf K *et al* 1993 The human myelin basic protein gene is included within a 179-kilobase transcription unit: expression in the immune and central nervous system. *Proc Natl Acad Sci USA* **90**: 10695–10699

Pribyl TM, Campagnoni CW, Kampf K *et al* 1996 Expression of the myelin proteolipid protein gene in human fetal thymus. *J Neuroimmunol* **67**: 125–130

Price P, Cuzner ML 1979 Proteinase inhibitors in cerebrospinal fluid in multiple sclerosis. *J Neurol Sci* **42**: 251–259

Priller J, Flügel A, Wehner T *et al* 2001 Targeting gene-modified hematopoietic cells to the central nervous system: use of green fluorescent protein uncovers microglial engraftment. *Nature Med* **7**: 1356–1361

Prineas JW 1975 Pathology of the early lesion in multiple sclerosis. *Hum Pathol* **6**: 531–554

Prineas JW 1979 Multiple sclerosis: presence of lymphatic capillaries and lymphoid tissue in the brain and spinal cord. *Science* **203**: 1123–1125

Prineas JW 1985 The neuropathology of multiple sclerosis. In: Koetsier JC (ed.) *Handbook of Clinical Neurology: Demyelinating Diseases*. Amsterdam: Elsevier, Vol 47, pp. 337–395

Prineas JW, Connell F 1979 Remyelination in multiple sclerosis. *Ann Neurol* **5**: 22–31

Prineas JW, Graham JS 1981 Multiple sclerosis: capping of surface immunoglobulin G on macrophages engaged in myelin breakdown. *Ann Neurol* **10**: 149–158

Prineas JW, McDonald WI 1997 Demyelinating disease. In: Graham DI, Lantos PL. *Greenfield's Neuropathology*, 6th edn. London: Arnold, pp. 813–896

Prineas JW, Wright RG 1978 Macrophages, lymphocytes, and plasma cells in the perivascular compartment in chronic multiple sclerosis. *Lab Invest* **38**: 409–421

Prineas JW, Kwon EE, Cho ES, Sharer LR 1984 Continual breakdown and regeneration of myelin in progressive multiple sclerosis plaques. *Ann NY Acad Sci* **436**: 11–32

Prineas JW, Kwon EE, Sharer LR, Cho E-S 1987 Massive early remyelination in acute multiple sclerosis. *Neurology* **37**: 109

Prineas JW, Kwon EE, Goldenberg PZ *et al* 1989 Multiple sclerosis: oligodendrocyte proliferation and differentiation in fresh lesions. *Lab Invest* **61**: 489–503

Prineas JW, Kwon EE, Goldenberg PZ *et al* 1990 Interaction of astrocytes and newly formed oligodendrocytes in resolving multiple sclerosis lesions. *Lab Invest* **63**: 624–636

Prineas JW, Barnard RO, Revesz T *et al* 1993a Multiple sclerosis: pathology of recurrent lesions. *Brain* **116**: 681–693

Prineas JW, Barnard RO, Kwon EE *et al* 1993b Multiple sclerosis: remyelination of nascent lesions. *Ann Neurol* **33**: 137–151

Prineas JW, Kwon EE, Cho ES *et al* 2001 Immunopathology of secondary–progressive multiple sclerosis. *Ann Neurol* **50**: 646–657

Pringle CE, Hudson AJ, Munoz DG, Kiernan JA, Brown WF, Ebers GC 1992 Primary lateral sclerosis: clinical features, neuropathology and diagnostic criteria. *Brain* **115**: 495–520

Pringle NP, Richardson WD 1993 A singularity of PDGF alpha receptor expression in the dorsoventral axis of the neural tube may define the origin of the oligodendrocyte lineage. *Development* **117**: 525–533

Pringle NP, Mudhar HS, Collarini EJ, Richardson WD 1992 PDGF receptors in the rat CNS: during late neurogenesis, PDGF alpha-receptor expression appears to be restricted to glial cells of the oligodendrocyte lineage. *Development* **115**: 535–551

Pringle NP, Guthrie S, Lumsden A, Richardson WD 1998 Dorsal spinal cord neuroepithelium generates astrocytes but not oligodendrocytes. *Neuron* **20**: 883–893

Pringle NP, Yu WP, Howell M *et al* 2003 FGFR3 expression by astrocytes and their precursors: evidence that astrocytes and oligodendrocytes originate in distinct neuroepithelial domains. *Development* **130**: 93–102

Prinjha R, Moore SE, Vinson M, Blake 2000 Inhibitor of neurite outgrowth in humans. *Nature* **403**: 383–384

PRISMS (Prevention of Relapses and Disability by Interferon-beta 1a Subsequently in Multiple Sclerosis) Study Group 1998 Randomised, double-blind, placebo-controlled study of interferon-beta 1a in relapsing–remitting multiple sclerosis: clinical results. *Lancet* **352**: 1498–1504

PRISMS Study Group and University of British Columbia MS MRI Analysis Group 2001 PRISMS-4: long-term efficacy of interferon-beta-1a in relapsing MS. *Neurology* **56**: 1628–1636

Probert L, Akassoglou K, Pasparakis M *et al* 1995 Spontaneous inflammatory demyelinating disease in transgenic mice showing central nervous system-specific expression of tumor necrosis factor. *Proc Natl Acad Sci USA* **92**: 11294–11298

Probert L, Eugster HP, Akassoglou K *et al* 2000 TNFR1 signalling is critical for the development of demyelination and the limitation of T-cell responses during immune-mediated CNS disease. *Brain* **123**: 2005–2019

Probst-Cousin S, Kowolik D, Kuchelmeister K *et al* 2002 Expression of annexin-1 in multiple sclerosis plaques. *Neuropath Appl Neurobiol* **28**: 292–300

Prochazka A, Gorassini M 1998 Ensemble firing of muscle afferents recorded during normal locomotion in cats. *J Physiol* **507**: 293–304

Proescholdt MA, Jacobson S, Tresser N *et al* 2003 Vascular endothelial growth factor is expressed in multiple sclerosis plaques and can induce inflammatory lesions in experimental allergic encephalomyelitis rats. *J Neuropathol Exp Neurol* **61**: 914–925

Propert DN, Bernard CCA, Simons MJ 1982 Gm allotypes in multiple sclerosis. *J Immunogenet* **9**: 359–361

Proudfoot AE 2002 Chemokine receptors: multifaceted therapeutic targets. *Nat Rev Immunol* **2**: 215

Proulx NL, Freedman MS, Chan JW *et al* 2003 Acute disseminated encephalomyelitis associated with *Pasteurella multocida* meningitis. *Can J Neurol Sci* **30**: 155–158

Provencale J, Bouldin TW 1992 Lupus-related myelopathy: report of three cases and review of literature. *J Neurol Neurosurg Psychiatry* **55**: 830–835

Provencher SW 1993 Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magn Reson Med* **30**: 672–679

Pryce G, Ahmed Z, Hankey D *et al* 2003 Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. *Brain* **126**: 2191–2202

Pryor W (ed.) 2004 *Virginia Woolf and the Raverats: A different sort of friendship*. Bath: Clear Books

Pryse-Phillips WEM 1986 The incidence and prevalence of multiple sclerosis in Newfoundland and Labrador, 1960–1984. *Ann Neurol* **20**: 323–328

Pryse-Phillips WEM, Chandra RK, Rose B 1984 Anaphylactoid reaction to methylprednisolone pulsed therapy for multiple sclerosis. *Neurology* **34**: 1119–1121

Pugliatti M, Sotgiu S, Solinas G *et al* 2001a Multiple sclerosis epidemiology in Sardinia: evidence for a true increasing risk. *Acta Neurol Scand* **103**: 20–26

Pugliatti M, Solinas G, Sotgiu S *et al* 2001b Multiple sclerosis distribution in northern Sardinia: spatial cluster analysis of prevalence. *Neurology* **58**: 277–282

Pujol J, Bello J, Deus J *et al* 1997 Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology* **49**: 1105–1110

Pulfrich von C 1922 Die Stereoskopie im Dienste der isochromen ünd heterochromen Photometrie. *Naturwissenschaften* **10**: 553–564, 569–574, 596–601, 714–722, 735–743, 751–761

Pulkkinen K, Luomala M, Kuusisto H *et al* 2004 Increase in CCR5 Delta32/Delta32 genotype in multiple sclerosis. *Acta Neurol Scand* **109**: 342–347

Purba JS, Raadsheer FC, Hofman MA *et al* 1995 Increased number of corticotrophin releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus of patients with multiple sclerosis. *Neuroendocrinology* **62**: 62–70

Purves Stewart J 1930 A specific vaccine treatment in disseminated sclerosis. *Lancet* **i**: 560–564

Putnam TJ 1935 Studies in multiple sclerosis. IV. Encephalitis and sclerotic plaques produced by venular obstruction. *Arch Neurol* **33**: 929–940

Putnam TJ 1936 Studies in multiple sclerosis VII: similarities between some forms of encephalomyelitis and multiple sclerosis. *Arch Neurol Psychiatry* **35**: 1289–1308

Putnam TJ 1938 The centenary of multiple sclerosis. *Arch Neurol Psychiatry* **40**: 806–813

Putnam TJ 1939 Criteria of effective treatment in multiple sclerosis. *J Am Med Assoc* **112**: 2488–2491

Putnam TJ, Adler A 1937 Vascular architecture of the lesions of multiple sclerosis. *Arch Neurol Psychiatry* **38**: 1–15

Qi Y, Cai J, Wu Y *et al* 2001 Control of oligodendrocyte differentiation by the Nkx2.2 homeodomain transcription factor. *Development* **128**: 2723–2733

Qi Y, Tan M, Hui CC, Qiu M 2003 Gli2 is required for normal Shh signaling and oligodendrocyte development in the spinal cord. *Mol Cell Neurosci* **23**: 440–450

Qin S, Cobbold SP, Pope H *et al* 1993 'Infectious' transplantation tolerance. *Science* **259**: 974–977

Qin Y, Duquette P, Zhang Y *et al* 1998 Clonal expansion and somatic hypermutation of V_H genes of B cells from cerebrospinal fluid in multiple sclerosis. *J Clin Invest* **102**: 1045–1050

Qin Y, Zhang DQ, Prat A *et al* 2000 Characterization of T cell lines derived from glatiramer-acetate-treated multiple sclerosis patients. *J Neuroimmunol* **108**: 201–206

Qiu J, Cai D, Dai H *et al* 2002 Spinal axon regeneration induced by elevation of cyclic AMP. *Neuron* **34**: 895–903

Quagliarello V, Scheld WM 1992 Bacterial meningitis: pathogenesis, pathophysiology and progress. *N Engl J Med* **327**: 864–872

Quan D, Pelak V, Tanabe J *et al* 2005 Spinal and cranial hypertrophic neuropathy in multiple sclerosis. *Muscle Nerve* **31**: 772–779

Quarles RH 1989 Glycoproteins of myelin and myelin forming cells. In: Margolis RU, Margolis RK (eds) *Neurobiology of Glycoconjugates*. New York: Plenum Press, pp. 243–275

Quasthoff S, Pojer C, Mori A *et al* 2003 No blocking effects of the pentapeptide QYNAD on Na+ channel subtypes expressed in Xenopus oocytes or action potential conduction in isolated rat sural nerve. *Neurosci Lett* **352**: 93–96

Quelvennec E, Bera O, Cabre P *et al* 2003 Genetic and functional studies in multiple sclerosis patients from Martinique attest for a specific and direct role of the HLA-DR locus in the syndrome. *Tissue Antigens* **61**: 166–171

Quesnel S, Feinstein A 2004 Multiple sclerosis and alcohol: a study of problem drinking. *Mult Scler* **10**: 197–201

Raabe TD, Suy S, Welcher A, DeVries GH 1997 Effect of neu differentiation factor isoforms on neonatal oligodendrocyte function. *J Neurosci Res* **50**: 755–768

Rabin J 1973 Hazard of influenza vaccine in neurologic patients. *J Am Med Assoc* **225**: 63–64

Rabins PV, Brooks BR, O'Donnell P *et al* 1986 Structural brain correlates of emotional disorder in multiple sclerosis. *Brain* **109**: 585–597

Racadot E, Rumbach L, Bataillard M *et al* 1993 Treatment of multiple sclerosis with anti-CD4 monoclonal antibody. *J Autoimmun* **6**: 771–786

Racke MK, Dhib-Jalbut S, Cannella B *et al* 1991 Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-β1. *J Immunol* **146**: 3012–3017

Racke MK, Cannella B, Albert P *et al* 1992 Evidence of endogenous regulatory function of transforming growth factor-beta 1 in experimental allergic encephalomyelitis. *Int Immunol* **4**: 615–620

Racke MK, Bonomo A, Scott DE *et al* 1994 Cytokine-induced immune deviation as a therapy for inflammatory autoimmune disease. *J Exp Med* **180**: 1961–1966

Radhakrishnan K, Ashok PP, Sridharan R, Mousa ME 1985 Prevalence and pattern of multiple sclerosis in Benghazi, North-Eastern Libya. *J Neurol Sci* **70**: 39–46

Radic MZ, Zouali M 1996 Receptor editing, immune diversification, and self-tolerance. *Immunity* **5**: 505–511

Rafalowska J, Krajewski S, Dolinska E, Dziewulska D 1992 Does damage to perivascular astrocytes in multiple sclerosis participate in blood brain barrier permeability. *Neuropathol Polska* **30**: 73–80

Raff MC 1992 Social controls on cell survival and cell death. *Nature* **356**: 397–400

Raff MC, Miller RH, Noble M 1983 A glial progenitor that develops *in vitro* into an astrocyte or an oligodendrocyte depending on culture medium. *Nature* **303**: 390–396

Raff MC, Williams BP, Miller RH 1984 The *in vitro* differentiation of a bipotential glial progenitor cell. *EMBO J* **3**: 1857–1864

Raff MC, Whitmore AV, Finn JT 2002 Axonal self-destruction and neurodegeneration. *Science* **296**: 868–871

Raine CS 1984 The neuropathology of myelin diseases. In: Morrell P (ed.) *Myelin*. New York: Plenum Press, pp. 259–310

Raine CS 1997 The Norton lecture: a review of the oligodendrocyte in the multiple sclerosis lesion. *J Neuroimmunol* **77**: 135–152

Raine CS, Wu E 1993 Multiple sclerosis: remyelination in acute lesions. *J Neuropathol Exp Neurol* **52**: 199–204

Raine CS, Powers JM, Suzuki K 1974a Acute multiple sclerosis: confirmation of paramyxovirus-like intranuclear inclusions. *Arch Neurol* **30**: 39–46

Raine CS, Snyder DH, Valsamis MP, Stone SH 1974b Chronic experimental encephalomyelitis in inbred guinea pigs: an ultrastructural study. *Lab Invest* **31**: 369–380

Raine CS, Scheinberg L, Waltz JM 1981 Multiple sclerosis: oligodendrocyte survival and proliferation in an active established lesion. *Lab Invest* **45**: 534–546

Raine CS, Cannella B, Dujivestijn AM, Cross AH 1990a Homing to central nervous

vasculature by antigen specific lymphocytes. II. Lymphocyte-endothelial cell adhesion during the initial stage of autoimmune demyelination. *Lab Invest* **63**: 476–489

Raine CS, Lee SC, Scheinberg LC *et al* 1990b Adhesion molecules on endothelial cells in the central nervous system: an emerging area in the neuroimmunology of multiple sclerosis. C*lin Immunol Immunopathol* **57**: 173–187

Raivich G, Bohatschek M, Kloss CUA *et al* 1999 Neuroglial activation repertoire in the injured brain: graded response, molecular mechanisms and cues to physiological function. *Brain Res Rev* **30**: 77–105

Rajan AJ, Gao Y-L, Raine CS, Brosnan CF 1996 A pathogenic role for γδ-T cells in relapsing–remitting experimental allergic encephalomyelitis in the SJL mouse. *J Immunol* **157**: 941–949

Rajan AJ, Klein JDS, Brosnan CF 1999 The effect of gamma-delta T cell depletion on cytokine gene expression. *J Immunol* **160**: 5955–5962

Rajda C, Bencsik K, Seres E *et al* 2003 A genome-wide screen for association in Hungarian multiple sclerosis. *J Neuroimmunol* **143**: 84–87

Rajewsky K 1996 Clonal selection and learning in the antibody system. *Nature* **381**: 751–758

Raknes G, Fernandes Filho JA, Pandey JP *et al* 2000 IgG allotypes and subclasses in Norwegian patients with multiple sclerosis. *J Neurol Sci* **175**: 111–115

Ramanathan M, Weinstock-Guttman B, Nguyen LT *et al* 2001 In vivo gene expression revealed by cDNA arrays: the pattern in relapsing–remitting multiple sclerosis patients compared with normal subjects. *J Neuroimmunol* **116**: 213–219

Ramer MS, Priestley JV, McMahon SB 2000 Functional regeneration of sensory axons into the adult spinal cord. *Nature* **403**: 312–316

Ramirez-Lassepas M, Tulloch JW, Quinones MR, Snyder BD 1992 Acute radicular pain as a presenting symptom in multiple sclerosis. *Arch Neurol* **49**: 255–258

Rammohan KW, Rosenberg JH, Lynn DJ *et al* 2002 Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry* **72**: 179–183

Ranscht B, Clapshaw PA, Price J *et al* 1982 Development of oligodendrocytes and Schwann cells studied with a monoclonal antibody against galactocerebroside. *Proc Natl Acad Sci USA* **79**: 2709–2713

Ransohoff RM 1999 Mechanisms of inflammation in MS tissue: adhesion molecules and chemokines. *J Neuroimmunol* **98**: 57–68

Ransohoff RM, Estes ML 1991 Astrocyte expression of major histocompatibility complex gene products in multiple sclerosis brain tissue obtained by stereotactic biopsy. *Arch Neurol* **48**: 1244–1246

Ransohoff RM, Kivisäkk P, Kidd G 2003 Three or more routes for leukocyte migration into the central nervous system. *Nature Rev Immunol* **3**: 569–581

Ranzato F, Perini P, Tzintzeva E *et al* 2003 Increasing frequency of multiple sclerosis in Padova, Italy: a 30 year epidemiological survey. *Mult Scler* **9**: 387–392

Rao AB, Richert N, Howard T *et al* 2002 Methylprednisolone effect on brain volume and enhancing lesions in MS before and during IFNbeta-1b. *Neurology* **59**: 688–694

Rao MS, Noble M, Mayer-Proschel M 1998 A tripotential glial precursor cell is present in the developing spinal cord. *Proc Natl Acad Sci USA* **95**: 3996–4001

Rao SM, Leo GJ 1988 Mood disorder and multiple sclerosis. *Arch Neurol* **45**: 247–248

Rao SM, Hammeke TA, McQuillen MP *et al* 1984 Memory disturbance in chronic progressive multiple sclerosis. *Arch Neurol* **41**: 625–631

Rao SM, Leo GJ, Haughton VM *et al* 1989a Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology* **39**: 161–166

Rao SM, Bernardin L, Leo GJ *et al* 1989b Cerebral disconnection in multiple sclerosis: relationship to atrophy of the corpus callosum. *Arch Neurol* **46**: 918–920

Rao SM, Leo GJ, Bernardin L, Unverzagt F 1991a Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns and predictions. *Neurology* **41**: 685–691

Rao SM, Leo GJ, Ellington L *et al* 1991b Cognitive dysfunction in multiple sclerosis. II Impact on employment and social functioning. *Neurology* **41**: 692–696

Rao SM, Grafman J, DiGiulio D *et al* 1993 Memory disturbance in multiple sclerosis: its relation to working memory, semantic encoding and implicit learning. *Neuropsychology* **7**: 364–374

Rapalino O, Lazarov-Spiegler O, Agranov E *et al* 1998 Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. *Nature Med* **4**: 814–821

Rasband MN, Shrager P 2000 Ion channel sequestration in central nervous system axons. *J Physiol* **525**: 63–73

Rasband MN, Trimmer JS 2001 Subunit composition and novel localization of K+ channels in spinal cord. *J Comp Neurol* **429**: 166–176

Rasband MN, Trimmer JS, Schwarz TL *et al* 1998 Potassium channel distribution, clustering, and function in remyelinating rat axons. *J Neurosci* **18**: 36–47

Rasband MN, Peles E, Trimmer JS *et al* 1999a Dependence of nodal sodium channel clustering on paranodal axoglial contact in the developing CNS. *J Neurosci* **19**: 7516–7528

Rasband MN, Trimmer JS, Peles E *et al* 1999b K+ channel distribution and clustering in developing and hypomyelinated axons of the optic nerve. *J Neurocytol* **28**: 319–331

Rasche D, Kress B, Schwark C *et al* 2004 Treatment of trigeminal neuralgia associated with multiple sclerosis: case report. *Neurology* **63**: 1714–1715

Rashid W, Parkes LM, Ingle GT *et al* 2004 Abnormalities of cerebral perfusion in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **75**: 1288–1293

Rasminsky M 1973 The effects of temperature on conduction in demyelinated single nerve fibers. *Arch Neurol* **28**: 287–292

Rasminsky M 1978 Ectopic generation of impulses and cross-talk in spinal nerve roots of 'dystrophic' mice. *Ann Neurol* **3**: 351–357

Rasminsky M 1980 Ephaptic transmission between single nerve fibres in the spinal nerve roots of dystrophic mice. *J Physiol* **305**: 151–169

Rasminsky M 1987 Spontaneous activity and cross-talk in pathological nerve fibers. *Res Publ Assoc Res Nerv Mental Dis* **65**: 39–49

Rasminsky M, Sears TA 1972 Internodal conduction in undissected demyelinated nerve fibres. *J Physiol* **227**: 323–350

Rasmussen HB, Geny C, Deforges L *et al* 1995 Expression of endogenous retroviruses in blood mononuclear cells and brain tissue from multiple sclerosis patients. *Mult Scler* **1**: 82–87

Rasmussen HB, Kelly MA, Francis DA, Clausen J 2000 Association between the endogenous retrovirus HRES-1 and multiple sclerosis in the United Kingdom – evidence of genetically different disease subsets? *Disease Markers* **16**: 101–104

Rasmussen HB, Kelly MA, Clausen J 2001a Additive effect of the HLA-DR15 haplotype on susceptibility to multiple sclerosis. *Mult Scler* **7**: 91–93

Rasmussen HB, Kelly MA, Clausen J 2001b Genetic susceptibility to multiple sclerosis: detection of polymorphic nucleotides and an intron in the 3' untranslated region of the major histocompatibility complex class II transactivator gene. *Hum Immunol* **63**: 371–377

Rasmussen HB, Kelly MA, Francis DA, Clausen J 2001c CTLA4 in multiple sclerosis: lack of genetic association in a European Caucasian population but evidence of interaction with HLA-DR2 among Shaghai Chinese. *J Neurol Sci* **184**: 143–147

Ravaglia S, Ceroni M, Moglia A *et al* 2004 Post-infectious and post-vaccinal acute disseminated encephalomyelitis occurring in the same patients. *J Neurol* **251**: 1147–1150

Rawson MD, Liversedge LA 1969 Treatment of retrobulbar neuritis with corticotrophin. *Lancet* **ii**: 222

Rawson MD, Liversedge LA, Goldfarb G, McGill BA 1966 Treatment of acute retrobulbar neuritis with corticotrophin. *Lancet* **ii**: 1044–1046

Ray CL, Dreizin IJ 1996 Bilateral optic neuropathy associated with influenza vaccination. *J Neuroophthalmol* **16**: 182–184

Raymond GV 2002 Progressive cerebral degeneration of childhood. In: Asbury AK, McKann GM, McDonald WI *et al* (eds)

Diseases of the Nervous System, 3rd edn. Cambridge: Cambridge University Press, pp. 1911–1921

Read CF 1932 Multiple sclerosis and Lhermitte's sign. *Arch Neurol Psychiatry* **27**: 227–228

Reboul J, Mertens C, Levillayer F *et al* 2000 Cytokines in genetic susceptibility to multiple sclerosis: a candidate gene approach. *J Neuroimmunol* **102**: 107–112

de Recondo A, Guichard JP 1997 Acute disseminated encephalomyelitis presenting as multiple cystic lesions. *J Neurol Neurosurg Psychiatry* **63**: 15

Reddy EP, Sandberg-Wollheim M, Mettus RV *et al* 1989 Amplification and molecular cloning of HTLV-1 sequences from DNA of multiple sclerosis patients. *Science* **243**: 529–533

Reddy H, Narayanan S, Arnoutelis R *et al* 2000 Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. *Brain* **123**: 2314–2320

Reddy H, Narayanan S, Woolrich M *et al* 2002 Functional brain reorganization for hand movement in patients with multiple sclerosis: defining distinct effects of injury and disability. *Brain* **125**: 2646–2657

Reder AT, Arnason BGW 1985 Immunology of multiple sclerosis. In: Koetsier JC (ed.) *Handbook of Clinical Neurology: Demyelinating Diseases*. Amsterdam: Elsevier, Vol 47, pp. 337–395

Reder AT, Arnason BG 1995 Trigeminal neuralgia in multiple sclerosis relieved by a prostraglandin E analogue. *Neurology* **45**: 1097–1100

Reder AT, Makowiec RL, Lowy MT 1994 Adrenalin size is increased in multiple sclerosis. *Arch Neurol* **51**: 151–154

Redford EJ, Hall SM, Smith KJ 1995 Vascular changes and demyelination induced by the intraneural injection of tumour necrosis factor. *Brain* **118**: 869–878

Redford EJ, Kapoor R, Smith KJ 1997 Nitric oxide donors reversibly block axonal conduction: demyelinated axons are especially susceptible. *Brain* **120**: 2149–2157

Reding M, La Rocca N 1987 Acute hospital care versus rehabilitation hospitalization for management of nonemergent complications in multiple sclerosis. *J Neurol Rehab* **1**: 13–17

Redlich E 1896 Zur Pathologie der multiplen Sklerose. *Arbeit Neurol Inst (Obersteiner Arbeit)* **IV**: 1–34

Rees LH, Grant DB, Wilson J 1975 Plasma corticotrophin levels in Addison–Schilder's disease. *Br Med J* **3**: 201–202

Regan D, Silver R, Murray JT 1977 Visual acuity and contrast sensitivity in multiple sclerosis: hidden visual loss. *Brain* **100**: 563–579

Reichert F, Rotshenker S 1996 Deficient activation of microglia during optic nerve degeneration. *J Neuroimmunol* **70**: 153–161

Reichert F, Rotshenker S 2003 Complement-receptor-3 and scavenger-receptor-AI/II mediated myelin phagocytosis in microglia and macrophages. *Neurobiol Dis* **12**: 65–72

Reidel MA, Stippich C, Heiland S *et al* 2003 Differentiation of multiple sclerosis plaques, subacute cerebral ischaemic infarcts, focal vasogenic oedema and lesions of subacute arteriosclerotic encephalopathy using magnetisation transfer measurements. *Neuroradiology* **45**: 289–294

Reik L 2002 *Neurosyphilis*. In: Asbury AK, McKann GM, McDonald WI *et al* (eds) *Diseases of the Nervous System*, 3rd edn. Cambridge: Cambridge University Press, pp. 1766–1776

Reik L, Burgdorfer W, Donaldson JO 1986 Neurologic abnormalities in Lyme disease without erythema chronicum migrans. *Am J Med* **81**: 73–78

Reimers D, Lopez-Toledano MA, Mason I *et al* 2001 Developmental expression of fibroblast growth factor (FGF) receptors in neural stem cell progeny: modulation of neuronal and glial lineages by basic FGF treatment. *Neurol Res* **23**: 612–621

Reindl M, Linington C, Brehm U *et al* 1999 Antibodies against the myelin oligodendrocyte glycoprotein and the myelin basic protein in multiple sclerosis and other neurological diseases: a comparative study. *Brain* **122**: 2047–2056

Reindl M, Khantane S, Ehling R *et al* 2003 Serum and cerebrospinal fluid antibodies to Nogo-A in patients multiple sclerosis and acute neurological disorders. *J Neuroimmunol* **145**: 139–147

Reingold SC 1990 Fatigue and multiple sclerosis. *MS News Mult Scler Soc Gt Br N Ireland* **142**: 30–31

Reinherz EL, Weiner HL, Hauser SL *et al* 1980 Loss of suppressor cells in active multiple sclerosis. *N Engl J Med* **303**: 125–129

Reis e Sousa C 2001 Dendritic cells as sensors of infection. *Immunity* **14**: 495–498

Reiser H, Stadecker MJ 1996 Costimulatory B7 molecules in the pathogenesis of infectious and autoimmune diseases. *N Engl J Med* **335**: 1369–1377

Reith KG, DiChiro G, Cromwell LD *et al* 1981 Primary demyelinating disease simulating glioma of the corpus callosum. *J Neurosurg* **55**: 620–624

Relvas JB, Setzu A, Baron W *et al* 2001 Expression of dominant-negative and chimeric subunits reveals an essential role for beta1 integrin during myelination. *Curr Biol* **11**: 1039–1043

Remlinger P 1928 Les paralysies due traitement antirabique. *Ann Inst Pasteur* **55 (Suppl)**: 35–68

Renfrew C 2002 Genetics and language in contemporary archaelogy. In: Cunliffe B, Davies W, Renfrew C. *Archaeology: The Widening Debate*. London: Oxford University Press, pp. 43–76

Renganathan M, Cummins TR, Hormuzdiar WN *et al* 2000 Nitric oxide is an autocrine regulator of Na^+ currents in axotomized C-type DRG neurons. *J Neurophysiol* **83**: 2431–2442

Renganathan M, Cummins TR, Waxman SG 2002 Nitric oxide blocks fast, slow, and persistent Na+ channels in C-type DRG neurons by S-nitrosylation. *J Neurophysiol* **87**: 761–775

Renganathan M, Gelderblom M, Black JA, Waxman SG 2003 Expression of Nav1.8 sodium channels perturbs the firing patterns of cerebellar Purkinje cells. *Brain Res* **959**: 235–242

Renno T, Zeine R, Girard JM, Gillani S, Dodelet V, Owens T 1994 Selective enrichment of Th1 $CD45RB^{low}$ $CD4^+$ T cells in autoimmune infiltrates in experimental allergic encephalomyelitis. *Int Immunol* **6**: 347–354

Renno T, Krakowski M, Piccirillo C *et al* 1995 TNF-alpha expression by resident microglia and infiltrating leukocytes in the central nervous system of mice with experimental allergic encephalomyelitis. Regulation by Th1 cytokines. *J Immunol* **154**: 944–953

Rep MH, Hintzen RQ, Polman CH, van Lier RA 1996 Recombinant interferon-beta blocks proliferation but enhances interleukin-10 secretion by activated human T-cells. *J Neuroimmunol* **67**: 111–118

Requena I, Arias M, López-Ibor L *et al* 1991 Cavernomas of the central nervous system: clinical and neuroimaging manifestations in 47 patients. *J Neurol Neurosurg Psychiatry* **54**: 590–594

Reth M 1989 Antigen receptor tail clue. *Nature* **338**: 383–384

Reubinoff BE, Itsykson P, Turetsky T *et al* 2001 Neural progenitors from human embryonic stem cells. *Nat Biotechnol* **19**: 1134–1140

Reulen JPH, Sanders EACM, Hogenhuis LAH 1983 Eye movement disorders in multiple sclerosis and optic neuritis. *Brain* **106**: 121–140

Reunanen K, Finnila S, Laaksonen M *et al* 2002 Chromosome 19q13 and multiple sclerosis susceptibility in Finland: a linkage and two-stage association study. *J Neuroimmunol* **126**: 134–142

Revel M, Chebath J, Mangelus M *et al* 1995 Antagonsim of interferon beta in interferon gamma: inhibition of signal transduction *in vitro* and reduction of serum levels in multiple sclerosis patients. *Mult Scler* **1**: S5–S11

Revel MP, Valiente E, Gray F *et al* 1993 Concentric MR patterns in multiple sclerosis: report of two cases. *J Neuroradiol* **20**: 252–257

Revesz T, Kidd D, Thompson AJ *et al* 1994 A comparison of the pathology of primary and secondary progressive multiple sclerosis. *Brain* **117**: 759–765

Revol A, Vighetto A, Confavreux C *et al* 1990 Myoclonies oculo-velo-palatines et sclérose en plaques. *Rev Neurol* **146**: 518–521

Revy P, Sospedra M, Barbour B, Trautmann A 2001 Functional antigen-independent synapses formed between T cells and dendritic cells. *Nat Immunol* **2**: 925–931

Reynier P, Penisson-Besnier I, Moreau C *et al* 1999 mtDNA haplotyping J: a contributing factor of optic neuritis. *Eur J Hum Genet* **7**: 404–406

Reynolds ES 1904 Some cases of family disseminated sclerosis. *Brain* **27**: 163–169

Reynolds JR (ed.) 1868 *A System of Medicine*, Vol 2. London: Macmillan

Reynolds R, Dawson M, Papadopoulos D *et al* 2002 The response of NG2-expressing oligodendrocyte progenitors to demyelination in MOG-EAE and MS. *J Neurocytol* **31**: 523–536

Reznik M, Franck G, Flandroy P, Lenelle J 1994 Syndrome médullaire pseudo-tumorale rélévant une sclérose en plaques probable débutante. Corrélations cliniques radiologiques et neuropathologiques. *Acta Neurol Belg* **94**: 8–16

Ribeton J 1919 *Etude clinique des douleurs à forme de décharge electrique consécutives aux traumatismes de la nuque*, Thèse de la Faculté de Médicine de l'Université de Paris, pp. 9–68

Ricard D, Stankoff B, Bagnard D *et al* 2000 Differential expression of collapsin response mediator proteins (CRMP/ULIP) in subsets of oligodendrocytes in the postnatal rodent brain. *Mol Cell Neurosci* **16**: 324–337

Rice CL, Vollmer TL, Bigland-Ritchie B 1992 Neuromuscular responses of patients with multiple sclerosis. *Muscle Nerve* **15**: 1123–1132

Rice CM, Scolding NJ 2004 Adult stem cells – reprogramming neurological repair? *Lancet* **364**: 193–199

Rice GP, Dickey C, Lesaux J, Vandervoort P, MacEwan L, Ebers GC 1995 Ondanestron for disabling cerebellar tremor. *Ann Neurol* **38**: 973

Rice GP, Ebers GC, Lublin FD, Knobler RL 1999 Ibuprofen treatment versus gradual introduction of interferon beta-1b in patients with MS. *Neurology* **52**: 1893–1895

Rice GP, Filippi M, Comi G 2000 Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. *Neurology* **54**: 1145–1155

Rice GP, Incorvaia B, Munari L *et al* 2001 Interferon in relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev* **4:** CD002002

Rice-Oxley M, Rees JR, Williams ES 1995 A prevalence survey of multiple sclerosis in Sussex. *J Neurol Neurosurg Psychiatry* **58**: 27–30

Rich MM, Pinter MJ, Kraner SD, Barchi RL 1998 Loss of electrical excitability in an animal model of acute quadriplegic myopathy. *Ann Neurol* **43**: 171–179

Richards M, Corte-Real H, Forster P *et al* 1996 Paleolithic and neolithic lineages in the European mitochondrial gene pool. *Am J Hum Genet* **59**: 185–203

Richards PT, Cuzner ML 1978 Proteolytic activity in CSF. *Adv Exper Med Biol* **100**: 521–527

Richardson JH, Wucherpfennig KW, Endo N *et al* 1989 PCR analysis of DNA from multiple sclerosis patients for the presence of HTLV-1. *Science* **246**: 821–823

Richert JR, Robinson ED, Deibler GE *et al* 1989 Human cytotoxic T-cell recognition of a synthetic peptide of myelin basic protein. *Ann Neurol* **26**: 342–346

Richert ND, Ostuni JL, Bash CN *et al* 2001 Interferon beta-1b and intravenous methylprednisolone promote lesion recovery in multiple sclerosis. *Mult Scler* **7**: 49–58

Richey ET, Kooi KA, Tourtellotte WW 1971 Visually evoked responses in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **34**: 275–280

Richie LI, Ebert PJR, Wu LC *et al* 2002 Imaging synapse formation during thymocyte selection: inability of CD3 to form a stable central accumulation during negative selection. *Immunity* **16**: 595–606

Ridet JL, Malhotra SK, Privat A, Gage FH 1997 Reactive astrocytes: cellular and molecular cues to biological function. *Trends Neurosci* **20**: 570–577

Ridley A, Schapira K 1961 Influence of surgical procedures on the course of multiple sclerosis. *Neurology* **11**: 81–92

Rieckmann P, Toyka KV 1999 Escalating immunotherapy of multiple sclerosis. Austrian–German–Swiss Multiple Sclerosis Therapy Consensus Group [MSTCG]. *Eur Neurol* **42**: 121–127

Rieckmann P, Nunke K, Burchhardt M *et al* 1993 Soluble intercellular adhesion molecule-1 in cerebrospinal fluid: an indicator for the inflammatory impairment of the blood-cerebrospinal fluid barrier. *J Neuroimmunol* **47**: 133–140

Rieckmann P, Michel U, Albrecht M *et al* 1995 Soluble forms of intercellular adhesion molecule-1 (ICAM-1) block lymphocyte attachment to cerebral endothelial cells. *J Neuroimmunol* **60**: 9–15

Rieckmann P, Weber F, Gunther A *et al* 1996 Pentoxyfilline, a phosphodiesterase inhibitor, induces immune deviation in patients with multiple sclerosis. *J Neuroimmunol* **64**: 193–200

Riedel K, Kempf VA, Bechtold A, Klimmer M 2001 Acute disseminated encephalomyelitis (ADEM) due to *Mycoplasma pneumoniae* infection in an adolescent. *Infection* **29**: 240–242

Rietberg MB, Brooks D, Uitdehaag BM, Kwakkel G 2005 Exercise therapy for multiple sclerosis. *Cochrane Database Syst Rev* **1:** CD003980

Riikonen R 1989 The role of infection and vaccination in the genesis of optic neuritis and multiple sclerosis in children. *Acta Neurol Scand* **80**: 425–431

Riikonen R, Donner M, Erkkilä H 1988 Optic neuritis in children and its relationship to multiple sclerosis: a clinical study of 21 children. *Dev Med Child Neurol* **30**: 349–359

Riise T 1997 Cluster studies in multiple sclerosis. *Neurology* **49 (Suppl 2)**: S27–S32

Riise T, Klauber MR 1992 Relationship between the degree of individual space-time clustering and the age at onset of disease among multiple sclerosis patients. *Int J Epidemiol* **21**: 528–532

Riise T, Gronning M, Aarli JA *et al* 1988 Prognostic factors for life expectancy in multiple sclerosis analysed by Cox-models. *J Clin Epidemiol* **41**: 1031–1036

Riise T, Gronning M, Klauber MR *et al* 1991 Clustering of residence of multiple sclerosis patients at age 13–20 years in Hordaland, Norway. *Am J Epidemiol* **133**: 932–939

Riise T, Gronning M, Fernández O *et al* 1992 Early prognostic factors for disability in multiple sclerosis, a European multicenter study. *Acta Neurol Scand* **85**: 212–218

Riise T, Nortdedt MW, Ascherio A 2003 Smoking is a risk factor for multiple sclerosis. *Neurology* **61**: 1122–1124

Riley D, Lang AE 1988 Hemiballismus in multiple sclerosis. *Mov Disord* **3**: 88–94

Rindfleisch E 1863 Histologisches Detail zur grauen Degeneration von Gehirn und Rückenmark. *Arch Pathol Anat Physiol Klin Med (Virchow)* **26**: 474–483

Ringel RA, Riggs JE, Brick JF 1988 Reversible coma with prolonged absence of pupillary and brainstem reflexes: an unusual response to a hypoxic-ischemic event in MS. *Neurology* **38**: 1275–1278

Rinne UK 1980 Tizanidine treatment of spasticity in multiple sclerosis and chronic myelopathy. *Curr Ther Res* **28**: 827–836

Rio J, Montalban X 2000 Ibuprofen treatment versus gradual introduction of interferon beta-1b in patients with MS. *Neurology* **54**: 1710

Rio J, Nos C, Marzo ME *et al* 1998 Low-dose steroids reduce flu-like symptoms at the initiation of IFNbeta-1b in relapsing–remitting MS. *Neurology* **50**: 1910–1912

del Río Hortega H 1939 The microglia. *Lancet* **1**: 1023–1026

del Río Hortega P 1921 Estudios sobre la neuroglia. La glia de escasas radiaciones (oligodendroglia). *Boletin Real Soc Esp Hist Nat* **21**: 63–92

Riordan-Eva P, Sanders MD, Govan GG *et al* 1995 The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. *Brain* **118**: 319–337

Risau W 1991 Induction of blood-brain barrier endothelial cell differentiation. *Ann NY Acad Sci* **633**: 405–419

Risch NJ 1990a Linkage strategies for genetically complex traits. I. Multilocus models. *Am J Hum Genet* **46**: 222–228

Risch NJ 1990b Linkage strategies for genetically complex traits. II. The power of affected relative pairs. *Am J Hum Genet* **46**: 229–241

Risch NJ 1990c Linkage strategies for genetically complex traits. III. The effect of marker polymorphism on the analysis of affected relative pairs. *Am J Hum Genet* **46**: 242–253

Risch NJ 2000 Searching for genetic determinants in the new millennium. *Nature* **405**: 847–856

Risch NJ, Merikangas K 1996 The future of genetic studies of complex human diseases. *Science* **273**: 1516–1517

Risch NJ, Teng J 1998 The relative power of family-based and case-control designs for linkage disequilibrium studies of complex human diseases I. DNA pooling. *Genome Res* **8**: 1273–1288

Rischbieth RHC 1968 Retrobulbar neuritis in the State of South Australia. *Proc Aust Soc Neurologists* **5**: 573–575

Riser M, Géraud G, Rascol A *et al* 1971 L'évolution de la sclérose en plaques: Etude de 203 observations suivies au-delà de 10 ans. *Rev Neurol* **124**: 479–486

Risien Russell JS 1899 Disseminate sclerosis. In: Clifford Allbutt T (ed.) *A System of Medicine*, Vol VII. London: Macmillan, pp. 50–96

Rissoan M-C, Soumelis V, Kadowaki N *et al* 1999 Reciprocal control of T helper cell and dendritic cell differentiation. *Science* **283**: 1183–1186

Ristori G, Carcassi C, Lai S *et al* 1997 HLA-DM polymorphisms do not associate with multiple sclerosis: an association study with analysis of myelin basic protein T cell specificity. *J Neuroimmunol* **77**: 181–184

Ristori G, Buzzi MG, Sabatini U *et al* 1999 Use of Bacille Calmette-Guérin (BCG) in multiple sclerosis. *Neurology* **53**: 1588–1589

Ristori G, Giunti D, Perna A *et al* 2000 Myelin basic protein intramolecular spreading without disease progression in a patient with multiple sclerosis. *J Neuroimmunol* **110**: 240–243

Ritchie AM, Gilden DH, Williamson AR *et al* 2004 Comparative analysis of the $CD19^+$ and $CD138^+$ cell antibody repertoires in the cerebrospinal fluid of patients with multiple sclerosis. *J Immunol* **173**: 649–656

Ritchie JM, Rang HP, Pellegrino R 1981 Sodium and potassium channels in demyelinated and remyelinated mammalian nerve. *Nature* **294**: 257–259

Ritter G, Poser S 1974 Epilepsie ünd multiple Sklerose. *Münchener Med Wochenschr* **116**: 1984–1986

Rivera-Quinones C, MacGavern D, Schmelzer JD *et al* 1998 Absence of neurological deficits following extensive demyelination in a class I-deficient murine model of multiple sclerosis. *Nature Med* **4**: 187–193

Rivers TM, Schwentker FF 1935 Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys. *J Exp Med* **61**: 689–702

Rivers TM, Sprunt DH, Berry GP 1933 Observations on attempts to produce acute disseminated encephalomyelitis in monkeys. *J Exp Med* **58**: 39–53

Rivkin MJ, Flax J, Mozell R *et al* 1995 Oligodendroglial development in human fetal cerebrum. *Ann Neurol* **38**: 92–101

Rizzo JF, Lessell S 1988 Risk of developing multiple sclerosis after uncomplicated optic neuritis: a long term prospective study. *Neurology* **38**: 185–190

Rizzo JF, Lessell S 1991 Optic neuritis and ischemic optic neuropathy: overlapping clinical profiles. *Arch Ophthalmol* **109**: 1668–1672

Rizzo M, Kellison IL 2004 Eyes, brains, and autos. *Arch Ophthalmol* **122**: 641–647

Rizzo MA, Kocsis JD, Waxman SG 1996 Mechanisms of paresthesiae, dysesthesiae, and hyperesthesiae: role of Na channel heterogeneity. *Eur Neurol* **36**: 3–12

Roberts DF 1986 Who are the Orcadians? *Anthrop Anzeiger* **44**: 93–104

Roberts DF 1991 Consanguinity and multiple sclerosis in Orkney. *Genet Epidemiol* **8**: 147–151

Roberts DF, Bates D 1982 The genetic contribution to multiple sclerosis: evidence from north east England. *J Neurol Sci* **54**: 287–293

Roberts DF, Papiha SS 1979 Polymorphisms and multiple sclerosis in Orkney. *J Epidemiol Commun Hlth* **33**: 236–242

Roberts DF, Roberts MJ 1979 Genetic analysis of multiple sclerosis in Orkney. *J Epidemiol Commun Hlth* **33**: 229–235

Roberts DF, Roberts MJ, Poskanser DC 1983 Genetic analysis of multiple sclerosis in Shetland. *J Epidemiol Commun Hlth* **37**: 281–285

Roberts MHW, Martin JP, McLelland L *et al* 1991 The prevalence of multiple sclerosis in the Southampton South West Hampshire Health Authority. *J Neurol Neurosurg Psychiatry* **54**: 55–59

Robertson NP, Deans J, Fraser M, Compston DAS 1995 Multiple sclerosis in the north Cambridgeshire districts of East Anglia. *J Neurol Neurosurg Psychiatry* **59**: 71–76

Robertson NP, Deans J, Fraser M, Compston DAS 1996a The south Cambridgeshire multiple sclerosis register: a three year update. *J Epidemiol Commun Hlth* **50**: 274–279

Robertson NP, Fraser M, Deans J *et al* 1996b Age adjusted recurrence risks for relatives of patients with multiple sclerosis. *Brain* **119**: 449–455

Robertson NP, Clayton D, Fraser MB *et al* 1996c Clinical concordance in sibling pairs with multiple sclerosis. *Neurology* **47**: 347–352

Robertson NP, O'Riordan JI, Chataway J *et al* 1997 Clinical characteristics and offspring recurrence rates of conjugal multiple sclerosis. *Lancet* **349**: 1587–1590

Robertson WF 1897 The normal histology and pathology of the neuroglia (in relation specially to mental diseases). *J Mental Sci* **43**: 733–752

Robertson WF 1899 On a new method of obtaining a black reaction in certain tissue elements of the central nervous system (platinum method). *Scot Med Surg J* **4**: 23–30

Robey E, Itano A, Fanslow WC, Fowlkes BJ 1994 Constitutive CD8 expression allows inefficient maturation of CD4 helper T cells in class II major histocompatibility complex mutant mice. *J Exp Med* **179**: 1997–2004

Robinson K, Rudge P 1977 Abnormalities of the auditory evoked potentials in patients with multiple sclerosis. *Brain* **100**: 19–40

Robinson WH, Fontoura P, Lee BJ *et al* 2003 Protein microarrays guide tolerizing DNA vaccine treatment of autoimmune encephalomyelitis. *Nat Biotechnol* **21**: 1033–1039

Rocca MA, Colombo B, Pratesi A *et al* 2000 A magnetization transfer imaging study of the brain in patients with migraine. *Neurology* **54**: 507–509

Rocca MA, Filippi M, Herzog J *et al* 2001 A magnetic resonance imaging study of the cervical cord in patients with CADASIL. *Neurology* **56**: 1392–1394

Rocca MA, Falini A, Colombo B *et al* 2002a Adaptive functional changes in the cerebral cortex of patients with nondisabling multiple sclerosis correlate with the extent of brain structural damage. *Ann Neurol* **51**: 330–339

Rocca MA, Matthews PM, Caputo D *et al* 2002b Evidence for widespread movement-associated functional MRI changes in patients with PPMS. *Neurology* **58**: 866–872

Rocca MA, Gavazzi C, Mezzapesa DM *et al* 2003a A functional magnetic resonance imaging study of patients with secondary progressive multiple sclerosis. *Neuroimage* **19**: 1770–1777

Rocca MA, Mezzapesa DM, Falini A *et al* 2003b Evidence for axonal pathology and adaptive cortical reorganization in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis. *Neuroimage* **18**: 847–855

Rocca MA, Iannucci G, Rovaris M *et al* 2003c Occult tissue damage in patients with primary progressive multiple sclerosis is independent of T2 visible lesions – a diffusion tensor MR study. *J Neurol* **250**: 456–460

Rocca MA, Pagani E, Ghezzi A *et al* 2003d Functional cortical changes in patients with multiple sclerosis and nonspecific findings on conventional magnetic resonance imaging scans of the brain. *Neuroimage* **19**: 826–836

Rocca MA, Falini A, Colombo B *et al* 2004 Is an altered pattern of cortical activations in patients at presentation with clinically isolated syndromes suggestive of MS influence the subsequent evolution to definite MS? *J Neurol* **251**: 51

Rocca MA, Mezzapesa DM, Ghezzi A *et al* 2005 A widespread pattern of cortical activations in patients at presentation with clinically isolated syndromes is associated with evolution to definite multiple sclerosis. *Am J Neuroradiol* **26**: 1136–1139

Rodewald H-R, Paul S, Haller C *et al* 2001 Thymus medulla consisting of epithelial islets each derived from a single progenitor. *Nature* **414**: 763–768

Rodgers MM, Mulcare JA, King DL *et al* 1999 Gait characteristics of individuals with multiple sclerosis before and after a 6-month aerobic training program. *J Rehab Res Development* **36**: 183–188

Rodgers JR, Cook RG 2005 MHC class Ib molecules bridge innate and acquired immunity. *Nature Rev Immunol* **5**: 459–471

Rodriguez D, Della Gaspera B, Zalc B *et al* 1997 Identification of a Val 145 Ile substitution in the human myelin oligodendrocyte

glycoprotein: lack of association with multiple sclerosis. *Mult Scler* **3**: 377–381
Rodriguez M 1992 Central nervous system demyelination and remyelination in multiple sclerosis and viral models of disease. *J Neuroimmunol* **40**: 255–263
Rodriguez M 2003 A function of myelin is to protect axons from subsequent injury: implications for deficits in multiple sclerosis. *Brain* **126**: 751–752
Rodriguez M, Lennon VA 1990 Immunoglobulins promote remyelination in the central nervous system. *Ann Neurol* **27**: 12–17
Rodriguez M, Lindsley MD 1992 Immunosuppression promotes CNS remyelination in chronic virus-induced demyelinating disease. *Neurology* **42**: 348–357
Rodriguez M, Miller DJ 1994 Immune promotion of central nervous system remyelination. *Prog Brain Res* **103**: 343–355
Rodriguez M, Scheithauer B 1994 Ultrastructure of multiple sclerosis. *Ultrastruct Pathol* **18**: 3–13
Rodriguez M, Sriram S 1988 Successful therapy of Theiler's virus-induced demyelination (DA strain) with monoclonal anti-Lyt-2 antibody. *J Immunol* **140**: 2950–2955
Rodriguez M, Lafuse WP, Leibowitz J, David CS 1986 Partial suppression of Theiler's virus induced demyelination *in vivo* by administration of monoclonal antibodies to immune-response gene products (Ia antigens). *Neurology* **36**: 964–970
Rodriguez M, Lennon VA, Benviste EN, Merrill JE 1987 Remyelination by oligodendrocytes stimulated by antiserum to spinal cord. *J Neuropathol Exp Neurol* **46**: 84–95
Rodriguez M, Wynn DR, Kimlinger TK, Katzmann JA 1990 Terminal component of complement (C9) in the cerebrospinal fluid of patients with multiple sclerosis and neurologic controls. *Neurology* **40**: 855–857
Rodriguez M, Karnes W, Bartleson JD, Pineda AA 1993a Plasma-pheresis in acute episodes of fulminant CNS inflammatory demyelination. *Neurology* **43**: 1100–1104
Rodriguez M, Scheithauer BW, Forbes G, Kelly PJ 1993b Oligodendrocyte injury is an early event in lesions of multiple sclerosis. *Mayo Clin Proc* **68**: 627–636
Rodriguez M, Prayoonwiwat N, Howe C, Sanborn K 1994a Proteolipid protein gene expression in demyelination and remyelination of the central nervous system: a model for multiple sclerosis. *J Neuropathol Exp Neurol* **53**: 136–143
Rodriguez M, Siva A, Ward J *et al* 1994b Impairment, disability, and handicap in multiple sclerosis: a population-based study in Olmsted County, Minnesota. *Neurology* **44**: 28–33
Rodriguez M, Siva A, Cross SA *et al* 1995 Optic neuritis: a population-based study in Olmsted County, Minnesota. *Neurology* **45**: 244–250
Rodriguez M, Miller DJ, Lennon VA 1996 Immunoglobulins reactive with myelin basic protein promote CNS remyelination. *Neurology* **46**: 538–545
Roed HG, Langkilde A, Sellebjerg F 2005 A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. *Neurology* **64**: 804–810
Rogers CL, Shetter AG, Ponce FA *et al* 2002 Gamma knife radiosurgery for trigeminal neuralgia associated with multiple sclerosis. *J Neurosurg* **97**: 529–532
Rokitansky K 1857 Uber Bindegewebswucherungen im Nervensysteme. Sitzungsberichte der mathematïsch – naturwissenschaftlichen. *Klass Kaiserlichen Akad Wiessenschaften Wien* **24**: 517–536
Rolak LA, Brown S 1990 Headaches and multiple sclerosis: a clinical study and review of the literature. *J Neurol* **237**: 300–302
Rollin H 1976 Geschmackstorungen bei multipler Sklerose [Gustatory disturbances in multiple sclerosis]. *Laryng Rhinol* **55**: 678–681
Romagnani S 1994 Lymphokine production by human T cells in disease states. *Annu Rev Immunol* **12**: 227–257
Romani A, Bergamaschi R, Versino M *et al* 2000 Circadian and hypothermia-induced effects on visual and auditory evoked potentials in multiple sclerosis. *Clin Neurophysiol* **111**: 1602–1606
Romberg A, Virtanen A, Aunola S *et al* 2004 Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. *Mult Scler* **10**: 212–218
Romi F, Krakenes J, Aarli JA, Tysnes OB 2004 Neuroborreliosis with vasculitis causing stroke-like manifestations. *Eur Neurol* **51**: 49–50
Romine J, Sipe J, Koziol J *et al* 1999 A double-blind, placebo-controlled, randomized trial of Cladribine in relapsing–remitting multiple sclerosis. *Proc Assoc Am Phys* **111**: 35–44
Ron MA, Feinstein A 1992 Multiple sclerosis and the mind. *J Neurol Neurosurg Psychiatry* **55**: 1–3
Ron MA, Logsdail SJ 1989 Psychiatric morbidity in multiple sclerosis: a clinical and MRI study. *Psychol Med* **19**: 887–895
Ron MA, Callanan MM, Warrington EK 1991 Cognitive abnormalities in multiple sclerosis: a psychometric and MRI study. *Psychol Med* **21**: 59–68
Roos RA, Wintzen AR, Vielvoye G, Polder TW 1991 Paroxysmal kinesigenic choreoathetosis as presenting symptom of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **54**: 657–658
Ropele S, Filippi M, Valsasina P *et al* 2005 Assessment and correction of B_1-induced errors in magnetization transfer ratio measurements. *Magn Reson Med* **53**: 134–140
Roper J, Schwarz JR 1989 Heterogeneous distribution of fast and slow potassium channels in myelinated rat nerve fibres. *J Physiol* **416**: 93–110
Rosati G 1989 The infectious hypothesis of multiple sclerosis in epidemiology. The time trend of the disease in Sardinia, Italy. In: Battaglia M (ed.) *Multiple Sclerosis Research*. Amsterdam: Elsevier, pp. 137–146
Rosati G 1994 Descriptive epidemiology of multiple sclerosis in Europe in the 1980s: a critical overview. *Ann Neurol* **36 (Suppl 2)**: S164–S174
Rosati G 2001 The prevalence of multiple sclerosis in the world: an update. *Neurol Sci* **22**: 117–139
Rosati G, Granieri E, Carreres M, Tola R 1980 Multiple sclerosis in southern Europe: a prevalence study in the socio-sanitary district of Copparo, northern Italy. *Acta Neurol Scand* **62**: 244–249
Rosati G, Granieri E, Carreras L *et al* 1981 Multiple sclerosis in northern Italy: prevalence in the province of Ferrara in 1978. *Ital J Neurol Sci* **2**: 17–23
Rosati G, Aiello I, Granieri E *et al* 1986 Incidence of multiple sclerosis in Macomer, Sardinia, 1912–1981: onset of the disease after 1950. *Neurology* **36**: 14–19
Rosati G, Aiello I, Pirastru MI *et al* 1987 Sardinia, a high-risk area for multiple sclerosis: a prevalence and incidence study in the district of Alghero. *Ann Neurol* **21**: 190–194
Rosati G, Aiello I, Mannu L *et al* 1988 Incidence of multiple sclerosis in the town of Sassari, Sardinia, 1965 to 1985: evidence for increasing occurrence of the disease. *Neurology* **38**: 384–388
Rose AS, Kuzma JW, Kurtzke JF *et al* 1970 Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs placebo: Final report. *Neurology* **20**: 1–19
Rose AS, Ellison GW, Myers LW, Tourtellotte WW 1976 Criteria for the clinical diagnosis of multiple sclerosis. *Neurology* **26**: 20–22
Rose FC 1970 The aetiology of optic neuritis. *Clin Sci* **39**: 17P
Rose J, Gerken S, Lynch S *et al* 1993 Genetic susceptibility in familial multiple sclerosis not linked to the myelin basic protein gene. *Lancet* **341**: 1179–1181
Rose JW, Watt HE, White AT, Carlson NG 2004 Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. *Ann Neurol* **56**: 864–867
Rosen JA 1965 Pseudo-isochromatic visual testing in the diagnosis of disseminated sclerosis. *Trans Am Neurol Assoc* **98**: 283–284
Rosen JA 1979 Prolonged azathioprine treatment of non-remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* **42**: 338–344
Rosenberg GA 1970 Meningoencephalitis following an influenza vaccination. *N Engl J Med* **283**: 1209
Rosenberg GA, Dencoff JE, Correa N, Reiners M, Ford CC 1996 Effect of steroids on CSF matrix metalloproteinases in multiple sclerosis: relation to blood-brain barrier injury. *Neurology* **46**: 1626–1632
Rosenberg JH, Shafor R 2005 Fatigue in multiple sclerosis: a rational approach to

evaluation and treatment. *Curr Neurol Neurosci Rep* **5:** 140–146
Rosenbluth J, Blakemore WF 1984 Structural specializations in cat of chronically demyelinated spinal cord axons as seen in freeze-fracture replicas. *Neurosci Lett* **48**: 171–177
Rosenbluth J, Tao-Cheng J-H, Blakemore WF 1985 Dependence of axolemmal differentiation on contact with glial cells in chronically demyelinated lesions of cat spinal cord. *Brain Res* **358**: 287–302
Rosengren LE, Lycke J, Andersen O 1995 Glial fibrillary acidic protein in CSF of multiple sclerosis patients: relation to neurological deficit. *J Neurol Sci* **133**: 61–65
Rösener M, Muraro PA, Riethmüller A *et al* 1997 2',3'-cyclic nucleotide 3'-phosphodiesterase: a novel candidate autoantigen in demyelinating autoimmune diseases. *J Neuroimmunol* **75**: 28–34
Ross C, Clemmesen KM, Svenson M *et al* 2000 Immunogenicity of interferon-beta in multiple sclerosis patients: influence of preparation, dosage, dose frequency, and route of administration. Danish Multiple Sclerosis Study Group. *Ann Neurol* **48**: 706–712
Rosse RB 1989 Fatigue in multiple sclerosis. *Arch Neurol* **46**: 841–842
Rossini PM, Di Stefano E, Boatta M, Basciani M 1985 Evaluation of sensory-motor 'central' conduction in normal subjects and in patients with multiple sclerosis. In: Morocutti C, Risso PA (eds) *Evoked Potentials: Neurophysiological and Clinical Aspects*. Amsterdam: Elsevier, pp. 115–130
Rossini PM, Pasqualetti P, Pozzilli C *et al* 2001 Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine. *Mult Scler* **7**: 354–358
Roström B, Link H 1981 Oligoclonal immunoglobulins in cerebrospinal fluid in acute cerebrovascular disease. *Neurology* **31**: 590–596
Roth M-P, Ballivet S, Descoins P *et al* 1994a Multiple sclerosis in the Pyrenees-Atlantiques: a case-control study conducted in the southwest of France. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 177–178
Roth M-P, Clayton J, Patois E, Alperovitch A 1994b Gender distributions in parents and children concordant for multiple sclerosis. *Neuroepidemiology* **13**: 211–215
Roth M-P, Nogueira L, Coppin H *et al* 1994c Tumour necrosis factor polymorphisms in multiple sclerosis: no additional association independent of HLA. *J Neuroimmunol* **51**: 93–99
Roth M-P, Riond J, Champagne E *et al* 1994d CRB-V gene usage in monozygotic twins discordant for multiple sclerosis. *Immunogenetics* **39**: 281–285
Roth M-P, Dolbois L, Borot N *et al* 1995 Myelin oligodendrocyte glycoprotein (MOG) gene polymorphisms and multiple sclerosis: no evidence of disease association with MOG. *J Neuroimmunol* **61**: 117–122
Roth NI, Coppin H, Descoins P *et al* 1991 HLA-DPB1 gene polymorphism and multiple sclerosis: a large case–control study in the southwest of France. *J Neuroimmunol* **34**: 215–222
Rothwell NJ, Luheshi G, Toulmond S 1996 Cytokines and their receptors in the central nervous system: physiology, pharmacology, and pathology. *Pharmacol Ther* **69**: 85–95
Rothwell PM, Charlton D 1998 High incidence and prevalence of multiple sclerosis in south-east Scotland: evidence of a genetic predisposition. *J Neurol Neurosurg Psychiatry* **64**: 730–735
Rothwell PM, McDowell Z, Wong, CK, Dorman PJ 1997 Doctors and patients don't agree: cross-sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *Br Med J* **314**: 1580–1583
Rotola A, Merlotti I, Caniatti L *et al* 2004 Human herpesvirus 6 infects the central nervous system of multiple sclerosis patients in the early stages of the disease. *Mult Scler* **10**: 348–354
Rotondi M, Oliviero A, Profice P *et al* 1998 Occurrence of thyroid autoimmunity and dysfunction throughout a nine-month follow-up in patients undergoing interferon-beta therapy for multiple sclerosis. *J Endocrinol Invest* **21:** 748–752
Rotondi M, Mazziotti G, Biondi B *et al* 2000 Long-term treatment with interferon-beta therapy for multiple sclerosis and occurrence of Graves' disease. *J Endocrinol Invest* **23**: 321–324
Rott O, Wekerle H, Fleischer B 1992 Protection from experimental allergic encephalomyelitis by application of a bacterial superantigen. *Int Immunol* **4**: 347–354
Rouher F, Plane C, Sole P 1969 Intérêt des potentiels évoqués visuels dans les affections du nerf optique. *Arch Ophtalomol (Paris)* **29**: 555–564
Roullet E, Verdier-Taillefer M-H, Amarenco P *et al* 1993 Pregnancy and multiple sclerosis: a longitudinal study of 125 remittent patients. *J Neurol Neurosurg Psychiatry* **56**: 1062–1065
Rousseau JJ, Lust C, Zangerle PF, Bigaignon G 1986 Acute transverse myelitis as presenting symptom of Lyme disease. *Lancet* **2**: 1222–1223
Roussel V, Yi F, Jauberteau MO *et al* 2000 Prevalence and clinical significance of anti-phopholipid antibodies in multiple sclerosis: a study of 89 patients. *J Autoimmun* **14**: 259–265
Rovaris M, Barnes D, Woodrofe N *et al* 1996 Patterns of disease activity in multiple sclerosis patients: a study with quantitative gadolinium enhanced brain MRI and cytokine measurements in different clinical subgroups. *J Neurol* **243**: 536–542
Rovaris M, Fillipi M, Minicucci L *et al* 2000a Cortical/subcortical disease burden and cognitive impairment in patients with multiple sclerosis. *Am J Neuroradiol* **21**: 402–408
Rovaris M, Viti B, Ciboddo C *et al* 2000b Brain involvement in systemic immune-mediated diseases: a magnetic resonance and magnetization transfer imaging study. *J Neurol Neurosurg Psychiatry* **68**:170–177
Rovaris M, Viti B, Ciboddo G *et al* 2000c Cervical cord magnetic resonance imaging findings in systemic immune-mediated diseases. *J Neurol Sci* **176**: 128–130
Rovaris M, Bozzali M, Rocca MA *et al* 2001a An MR study of tissue damage in the cervical cord of patients with migraine. *J Neurol Sci* **183**: 43–46
Rovaris M, Bozzali M, Santuccio G *et al* 2001b In vivo assessment of the brain and cervical cord pathology of patients with primary progressive multiple sclerosis. *Brain* **124**: 2540–2549
Rovaris M, Comi G, Rocca M *et al* and the European/Canadian Glatiramer Acetate Study Group 2001c Short term brain volume change in relapsing–remitting multiple sclerosis: effect of glatiramer acetate and implications. *Brain* **124**: 1803–1812
Rovaris M, Comi G, Sormani MP *et al* 2001d Effects of seasons on magnetic resonance imaging-measured disease activity in patients with multiple sclerosis. *Ann Neurol* **49**: 415–417
Rovaris M, Bozzali M, Iannucci G *et al* 2002a Assessment of normal-appearing white and gray matter in patients with primary progressive multiple sclerosis: a diffusion-tensor magnetic resonance imaging study. *Arch Neurol* **59**: 1406–1412
Rovaris M, Codella M, Moiola L *et al* 2002b Effect of glatiramer acetate on MS lesions enhancing at different gadolinium doses. *Neurology* **59**: 1429–1432
Rovaris M, Holtmannspotter M, Rocca MA *et al* 2002c Contribution of cervical cord MRI and brain magnetization transfer imaging in the assessment of individual patients with multiple sclerosis: a preliminary study. *Mult Scler* **8**: 52–58
Rowe VD, Wang D, John HA *et al* 2003 Rescue therapy with high dose intravenous methotrexate in MS patients worsening despite Avonex therapy. *Neurology* **60**: A149–A150
Rowen L, Koop BF, Hood L 1996 The complete 685-kilobase DNA sequence of the human b T cell receptor locus. *Science* **272**: 1755–1762
Roxburgh RH, Seaman SR, Masterman T *et al* 2005a Multiple sclerosis severity score: ranking disability at similar duration to rate disease severity. *Neurology* **64**: 1144–1151
Roxburgh RH, Sawcer SJ, Meranian M *et al* 2005b Multiple sclerosis and CTLA-4: different polymorphisms of this gene may predispose to different autoimmune diseases (submitted)
Rozza L, Bortolotti P, Sica A *et al* 1993 Kinesigenic dystonia as the first manifestation of multiple sclerosis with cervical and brainstem lesions. *Eur Neurol* **33**: 331–332

Rubio JP, Bahlo M, Butzkueven H *et al* 2002 Genetic dissection of the HLA region using haplotypes of Tasmanian with multiple sclerosis. *Am J Hum Genet* **70**: 1125–1137

Rubio JP, Bahlo M, Tubridy N *et al* 2004 Extended haplotype analysis in the HLA complex reveals an increased frequency of the HFE-C282Y mutation in individuals with multiple sclerosis. *Hum Genet* **114** : 573–580

Rubio N, Rodriguez R, Arevalo MA 2004 In vitro myelination by oligodendrocyte precursor cells transfected with the neurotrophin-3 gene. *Glia* **47**: 78–87

Rucker CW 1944a Sheathing of the retinal veins in multiple sclerosis. *Mayo Clin Proc* **19**: 176–178

Rucker CW 1944b Sheathing of the retinal veins in multiple sclerosis. *J Am Med Assoc* **127**: 970–973

Rucker CW 1947 Retinopathy of multiple sclerosis. *Trans Am Ophthalmol Soc* **45**: 564–570

Rucker CW 1972 Sheathing of the retinal veins in multiple sclerosis: review of pertinent literature. *Mayo Clin Proc* **47**: 335–340

Rudd Bosch JLR, Groen J 1996 treatment of refractory urge urinary incontinence with sacral spinal nerve stimulation in multiple sclerosis patients. *Lancet* **348**: 717–719

Rudge JS, Silver J 1990 Inhibition of neurite outgrowth on astroglial scars *in vitro*. *J Neurosci* **10**: 3594–3603

Rudge PR 1973 Optic neuritis as a complication of carcinoma of the breast. *Proc R Soc Med* **66**: 106–107

Rudge PR 1999 Are clinical trials of therapeutic agents for MS long enough? *Lancet* **353**: 1033–1034

Rudge PR, Koetsier JC, Mertin J *et al* 1989 Randomised double blind controlled trial of cyclosporin in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **52**: 559–565

Rudge PR, Ali A, Cruickshank JK 1991 Multiple sclerosis, tropical spastic paraplegia and HTLV-1 infection in Afro-Caribbean patients in the United Kingdom. *J Neurol Neurosurg Psychiatry* **54**: 689–694

Rudge PR, Miller DH, Crimlisk H, Thorpe J 1995 Does interferon beta cause initial exacerbation of multiple sclerosis? *Lancet* **345**: 580

Rudick RA 1995 Pregnancy and multiple sclerosis. *Arch Neurol* **52**: 849–850

Rudick RA, Barna BP 1990 Serum interleukin 2 and soluble interleukin 2 receptor in patients with multiple sclerosis who are experiencing severe fatigue. *Arch Neurol* **47**: 254–255

Rudick RA, Bidlack JM, Knutson SW 1985 Multiple sclerosis: cerebrospinal fluid immune complexes that bind C1q. *Arch Neurol* **42**: 856–858

Rudick RA, Schiffer RB, Schwetz KM, Herndon RM 1986 Multiple sclerosis: the problem of incorrect diagnosis. *Arch Neurol* **43**: 578–583

Rudick RA, Breton D, Krall RL 1987 The GABA-agonist progabide for spasticity in multiple sclerosis. *Arch Neurol* **44**: 1033–1036

Rudick RA, Antel J, Confavreux C *et al* 1996a Clinical outcomes assessment in multiple sclerosis. *Ann Neurol* **40**: 469–479

Rudick RA, Ranschoff RM, Peppler R *et al* 1996b Interferon beta induces interleukin-10 expression: relevance to multiple sclerosis. *Ann Neurol* **40**: 618–627

Rudick RA, Antel J, Confavreax C *et al* 1997a Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force. *Ann Neurol* **42**: 379–382

Rudick RA, Cohen JA, Weinstock-Guttman B *et al* 1997b Management of multiple sclerosis. *N Engl J Med* **337**: 1604–1611

Rudick RA, Goodkin DE, Jacobs LD *et al* 1997c Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. *Neurology* **49**: 358–363

Rudick RA, Simonian NA, Alam JA *et al* 1998a Incidence and significance of neutralizing antibodies to interferon beta-1a in multiple sclerosis. Multiple Sclerosis Collaborative Research Group (MSCRG). *Neurology* **50**: 1266–1272

Rudick RA, Ranschoff RM, Lee JC *et al* 1998b *In vivo* effects of interferon beta-1a on immunosuppressive cytokines in multiple sclerosis *Neurology* **50**: 1294–300

Rudick RA, Fischer E, Lee JC *et al* 1999 Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing–remitting MS. Multiple Sclerosis Collaborative Research Group. *Neurology* **53**: 1698–1704

Rudick RA, Cutter G, Reingold S 2002 The Multiple Sclerosis Functional Composite: a new clinical outcome measure for multiple sclerosis trials. *Mult Scler* **8**: 359–365

Rudick RA, Cookfair DL, Griffin J *et al* 2003 Interferons in relapsing remitting multiple sclerosis. *Lancet* **361**: 1824; author reply 1824–1825

Ruegg SJ, Buhlmann M, Renaud S *et al* 2004 Cervical dystonia as first manifestation of multiple sclerosis. *J Neurol* **251**: 1408–1410

Ruge D, Brochner R, Daris L 1958 A study of the treatment of 637 patients with trigeminal neuralgia. *J Neurosurg* **15**: 528–536

Ruggieri M, Polizzi A, Pavone L, Grimaldi LME 1999 Multiple sclerosis in children under 6 years of age. *Neurology* **53**: 478–484

Rush JA 1980 Retrobulbar optic neuritis in sarcoidosis. *Ann Ophthalmol* **12**: 390–394

Ruiz P, Garren H, Hirschberg DL *et al* 1999 Microbial epitopes act as altered peptide ligands to prevent experimental autoimmune encephalomyelitis. *J Exp Med* **189**: 1275–1283

Rumsby MG 1978 Organization and structure in central nerve myelin. *Biochem Soc Trans* **6**: 448–462

Runmarker B, Andersen O 1993 Prognostic factors in a multiple sclerosis incident cohort with twenty-five years of follow-up. *Brain* **116**: 117–134

Runmarker B, Andersen O 1995 Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis. *Brain* **118**: 253–261

Runmarker B, Martinsson T, Wahlstrom J, Andersen O 1994a HLA and prognosis in multiple sclerosis. *J Neurol* **241**: 385–390

Runmarker B, Andersson C, Oden A, Andersen O 1994b Prediction of outcome in multiple sclerosis based on multivariate models. *J Neurol* **241**: 597–604

Ruprecht K, Warmuth-Metz M, Waespe W, Gold R 2002 Symptomatic hyperekplexia in a patient with multiple sclerosis. *Neurology* **58**: 503–504

Rush JA, Younge BR 1981 Paralysis of cranial nerves III, IV and VI. *Arch Ophthalmol* **99**: 76–79

Rushton D 1975 Use of Pulfrich pendulum for detecting abnormal delay in the visual pathway in multiple sclerosis. *Brain* **98**: 283–296

Rushton JG, Olafson RA 1965 Trigeminal neuralgia associated with multiple sclerosis. *Arch Neurol* **13**: 383–386

Rushton WAH 1937 Initiation of the propagated disturbance. *Proc R Soc Lond Series B: Biol Sci* **124**: 210–243

Rusin JA, Vezina G, Chadduck WM, Chandra RS 1995 Tumoral multiple sclerosis of the cerebellum in a child. *Am J Neuroradiol* **16**: 1164–1166

Russell DS 1955 The nosological unity of acute haemorrhagic leucoencephalitis and acute disseminated encephalomyelitis. *Brain* **78**: 369–376

Russo R, Tenenbaum S, Morena M, Battagliotti C 2000 Interferon-beta 1a induced juvenile chronic arthritis in genetically predisposed young patient with multiple sclerosis: comment on the case report by Levesque *et al*. *Arthritis Rheum* **43**: 1190

Rutschmann OT, McCrory DC, Matchar DB *et al* 2002 Immunization and MS: a summary of published evidence and recommendations. *Neurology* **59**: 1837–1843

Ruutianen J, Salonen R, Halonen P *et al* 1991 Treatment of acute exacerbations in early multiple sclerosis: cyclosporin A or prednisolone. *Acta Neurol Scand* **83**: 52–54

Ryder LP, Anderson E, Svejgaard A 1978 An HLA map of Europe. *Hum Heredity* **28**: 171–200

Saab CY, Craner MJ, Kataoka Y, Waxman SG 2004 Abnormal Purkinje cell activity in vivo in experimental allergic encephalomyelitis. *Exp Brain Res* **158**: 1–8

Saarela J, Schoenberg Fejzo M, Chen D *et al* 2002 Fine mapping of a multiple sclerosis locus to 2.5 Mb on chromosome 17q22-q24. *Hum Mol Gen* **11**: 2257–2267

Saarela J, Chen D, Chi WS *et al* 2003 The physical map of the multiple sclerosis susceptibility on chromosome 17q22–24 exposes blocks of segmental duplication. *Am J Hum Genet* **71 (Suppl)**: 151 (abstract)

Sacconi S, Salviati L, Merelli E 2001 Acute disseminated encephalomyelitis associated

with hepatitis C virus infection. *Arch Neurol* **58**: 1679–1681
Sachidanandam R, Weissman D, Schmidt SC *et al* 2001 A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* **409**: 928–933
Sackett DL, Haynes RB, Tugwell P 1985 *Clinical Epidemiology: A Basic Science for Clinical Medicine*. Boston: Little, Brown, pp. 161–162
Sackett DL, Straus SE, Richardson WS *et al* 2000 *Evidence-Based Medicine. How to Practice and Teach EBM*, 2nd edn. Toronto: Churchill Livingstone
Sacks JG, Melen O 1975 Bitemporal visual field defects in presumed multiple sclerosis. *J Am Med Assoc* **234**: 69–72
Sadatipour BT, Greer JM, Pender MP 1998 Increased circulating antiganglioside antibodies in primary and secondary progressive multiple sclerosis. *Ann Neurol* **44**: 980–983
Sadeghi-Nejad A, Senior B 1990 Adrenomyeloneuropathy presenting as Addison's disease in childhood. *N Engl J Med* **322**: 13–16
Sadeh M, Shacked I, Rappaport ZH, Tadmor R 1982 Surgical extirpation of a venous angioma of the medulla oblongata simulating multiple sclerosis. *Surg Neurol* **17**: 334–335
Sadeh M, Kuritzky A, Ben-David E, Goldhammer Y 1992 Adult metachromatic leukodystrophy with an unusual relapsing–remitting course. *Postgrad Med J* **68**: 192–195
Sadlack B, Merz H, Schorle H *et al* 1993 Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell* **75**: 253–261
Sadovnick AD 1982 Concordance in twins and recurrence in siblings of multiple sclerosis. *Lancet* **i**: 1068
Sadovnick AD 1994 Genetic epidemiology of multiple sclerosis: a survey. *Ann Neurol* **36 (Suppl 2)**: S194–S203
Sadovnick AD, Baird PA 1988 The familal nature of multiple sclerosis: age-corrected empiric recurrence risks for children and siblings of patients. *Neurology* **38**: 990–991
Sadovnick AD, Ebers GC 1993 Epidemiology of multiple sclerosis: a critical overview. *Can J Neurol Sci* **20**: 17–29
Sadovnick AD, Scheifele DW 2000 School-based hepatitis B vaccination programme and adolescent multiple sclerosis. *Lancet* **355**: 549–550
Sadovnick AD, Yee IM 1994 Season of birth in multiple sclerosis. *Acta Neurol Scand* **89**: 190–191
Sadovnick AD, Baird PA, Ward RH 1988 Multiple sclerosis; updated risks for relatives. *Am J Med Genet* **29**: 533–541
Sadovnick AD, Paty DW, Yannakoulias G 1989 Concurrence of multiple sclerosis and inflammatory bowel disease. *N Engl J Med* **321**: 763–764
Sadovnick AD, Bulman D, Ebers GC 1991a Parent child concordance in multiple sclerosis. *Ann Neurol* **29**: 252–255
Sadovnick AD, Eisen K, Ebers GC, Paty DW 1991b Cause of death in patients attending multiple sclerosis clinics. *Neurology* **41**: 1193–1196
Sadovnick AD, Ebers GC, Wilson RW, Paty DW 1992 Life expectancy in patients attending multiple sclerosis clinics. *Neurology* **42**: 991–994
Sadovnick AD, Armstrong H, Rice GPA *et al* 1993 A population-based study of multiple sclerosis in twins: update. *Ann Neurol* **33**: 281–285
Sadovnick AD, Eisen K, Hashimoto SA *et al* 1994 Pregnancy and multiple sclerosis: a prospective study. *Arch Neurol* **51**: 1120–1124
Sadovnick AD, Ebers GC, Dyment DA, Risch N, the Canadian Collaborative Study Group 1996a Evidence for genetic basis of multiple sclerosis. *Lancet* **347**: 1728–1730
Sadovnick AD, Remick RA, Allen J *et al* 1996b Depression and multiple sclerosis. *Neurology* **46**: 628–632
Sadovnick AD, Yee IM, Ebers GC, Risch N 1998 Effect of age at onset and parental disease status on sibling risks for MS. *Neurology* **50**: 719–723
Sadovnick AD, Yee IM, Ebers GC, Canadian Collaborative Study Group 2000 Factors influencing sib risks for multiple sclerosis. *Clin Genet* **58**: 431–435
Sadovnick AD, Yee IM, Ebers GC, Canadian Collaborative Study Group 2001 Recurrence risks to sibs of MS index cases: impact of consanguineous matings. *Neurology* **56**: 784–785
Safronov BV, Kampe K, Vogel W 1993 Single voltage-dependent potassium channels in rat peripheral nerve membrane. *J Physiol* **460**: 675–691
Sagar HJ, Warlow CP, Sheldon PWE, Esiri MM 1982 Multiple sclerosis with clinical and radiological features of cerebral tumour. *J Neurol Neurosurg Psychiatry* **45**: 802–808
Sahlas DJ, Miller SP, Guerin M *et al* 2000 Treatment of acute disseminated encephalomyelitis with intravenous immunoglobulin. *Neurology* **54**: 1370–1372
Sahrbacher UC, Lechner F, Eugster H-P *et al* 1998 Mice with an inactivation of the inducible nitric oxide synthase gene are susceptible to experimental autoimmune encephalomyelitis. *Eur J Immunol* **28**: 1332–1338
Said G, Lacroix C, Plante-Bordeneuve V *et al* 2002 Nerve granulomas and vasculitis in sarcoid peripheral neuropathy: a clinicopathological study of 11 patients. *Brain* **125**: 264–275
Saida T, Tashiro K, Itoyama Y *et al* 2005 Interferon beta-1b is effective in Japanese RRMS patients: a randomized, multicenter study. *Neurology* **64**: 621–630
Saini HS, Gorse KM, Boxer LM, Sato-Bigbee C 2004 Neurotrophin-3 and CREB-mediated signaling pathway regulate Bc1–2 expression in oligodendrocyte progenitor cells. *J Neurochem* **89**: 951–961
Saito S, Naito S, Kawanami S, Kuroiwa Y 1976 HLA studies on multiple sclerosis in Japan. *Neurology* **26 (Part 2)**: 49
Saiz A, Marcos MA, Graus F *et al* 2001 No evidence of CNS infection with *Chlamydia pneumoniae* in patients with multiple sclerosis. *J Neurol* **248**: 617–618
Saiz A, Blanco Y, Carreras E *et al* 2004 Clinical and MRI outcome after autologous hematopoietic stem cell transplantation in MS. *Neurology* **62**: 282–284
Sajantila A, Lahermo P, Anttinen T *et al* 1995 Genes and language in Europe: an analysis of mitochondrial lineages. *Genome Res* **5**: 42–52
Sajantila A, Salem AH, Savolainen P *et al* 1996 Paternal and maternal DNA lineages reveal a bottleneck in the founding of the Finnish population. *Proc Natl Acad Sci USA* **93**: 12035–12039
Sakaguchi S 2000 Regulatory T cells: key controllers of immunological self tolerance. *Cell* **101**: 455–458
Sakaguchi S, Sakaguchi N 2000 Role of genetic factors in organ specific autoimmune diseases induced by manipulating the thymus or T cells, and not self-antigens. *Rev Imunogenet* **2**: 147–153
Sakaguchi S, Sakaguchi N, Asano M *et al* 1995 Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor a-chains (CD25): breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol* **155**: 1151–1164
Sakurai M, Kanazawa I 1999 Positive symptoms in multiple sclerosis: their treatment with sodium channel blockers, lidocaine and mexiletine. *J Neurol Sci* **162**: 162–168
Salama HH, Hong J, Zang YC *et al* 2003 Blocking effects of serum reactive antibodies induced by glatiramer acetate treatment in multiple sclerosis. *Brain* **126**: 2638–2647
Salemi G, Ragonese P, Aridon P *et al* 2000a Incidence of multiple sclerosis in Bagheria City, Sicily, Italy. *Neurol Sci* **21**: 361–365
Salemi G, Ragonese P, Aridon P *et al* 2000b Is season of birth associated with multiple sclerosis? *Acta Neurol Scand* **101**: 381–383
Salemi G, Callari G, Gammino M *et al* 2004 The relapse rate of multiple sclerosis changes during pregnancy: a cohort study. *Acta Neurol Scand* **110**: 23–26
Salier JP, Sesboue R, Martin-Mondiere C *et al* 1986 Combined influences of Gm and HLA phenotypes upon multiple sclerosis susceptibility and severity. *J Clin Invest* **78**: 533–538
Sallstom T 1942 Occurrence and distribution of multiple sclerosis in Sweden: geographic pathology of multiple sclerosis. *Acta Med Scand* **137 (Suppl)**: 1–14
Sallusto F, Lanzavecchia A, Mackay CR 1998 Chemokines and chemokine receptors in T cell priming and Th1/Th2 mediated responses. *Immunol Today* **19**: 568–574
Sallusto F, Lenig D, Förster R *et al* 1999 Two subsets of memory T lymphocytes with

distinct homing potentials and effector functions. *Nature* **401**: 708–712
Salmaggi A, Sandberg-Wollheim M 1993 Monocyte phenotype in blood and cerebrospinal fluid: compartment specific pattern is unrelated to neurological disease. *J Neurol Sci* **120**: 201–207
Salmaggi A, Corsini E, La Mantia L *et al* 1997 Immunological monitoring of azathioprine treatment in multiple sclerosis patients. *J Neurol* **244**: 167–174
Salmi A, Reunanen M, Ilonen J, Panelius M 1983 Intrathecal antibody synthesis to virus antigens in multiple sclerosis. *Clin Exp Immunol* **52**: 241–249
Salomon B, Bluestone JA 2001 Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. *Annu Rev Immunol* **19**: 225–252
Salonen R, Ilonen J, Reunanen M, Salmi A 1982 Defective production of interferon-alpha associated with HLA-DW2 antigen in stable multiple sclerosis. *J Neurol Sci* **55**: 197–206
Salvetti M, Ristori G, D'Amato M *et al* 1993 Predominant and stable T-cell responses to regions of myelin basic protein can be detected in individual patients with multiple sclerosis. *Eur J Immunol* **23**: 1232–1239
Salvetti M, Pisani A, Bastianello S *et al* 1995 Clinical and MRI assessment of disease activity in patients with multiple sclerosis after influenza vaccination. *J Neurol* **242**: 143–146
Salvi F, Mascalchi M, Plasmati R *et al* 1992 Multiple lesions in cerebral white matter in two young adults with thoracic extramedullary tumours. *J Neurol Neurosurg Psychiatry* **55**: 216–218
Samkoff LM, Daras M, Tuchman AJ, Koppel BS 1997 Amelioration of refractory dysestheic limb pain in multiple sclerosis by gabapentin. *Neurology* **49**: 304–305
Samoilova EB, Horton JL, Hilliard B *et al* 1998a IL-6-deficient mice are resistant to experimental autoimmune encephalomyelitis: roles of IL-6 in the activation and differentiation of autoreactive T cells. *J Immunol* **161**: 6480–6486
Samoilova EB, Horton JL, Chen YH 1998b Experimental autoimmune encephalomyelitis in intercellular adhesion molecule-1-deficient mice. *Cell Immunol* **190**: 83–89
Sanai N, Tramontin AD, Quinones-Hinojosa E *et al* 2004 Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature* **427**: 740–744
Sanchez T, Hassinger L, Paskevich PA *et al* 1996 Oligodendroglia regulate the regional expansion of axon calibre and local accumulation of neurofilaments during development independent of myelin formation. *J Neurosci* **16**: 5095–5105
Sanchez-Ramos J, Song S, Cardozo-Pelaez F *et al* 2000 Adult bone marrow stromal cells differentiate into neural cells in vitro. *Exp Neurol* **164**: 247–256
Sandberg-Wollheim M 1975 Optic neuritis: studies on the cerebrospinal fluid in relation to clinical course in 61 patients. *Acta Neurol Scand* **52**: 167–178
Sandberg-Wollheim M 1983 Lymphocyte populations in the cerebrospinal fluid and peripheral blood of patients with multiple sclerosis and optic neuritis. *Neurology* **17**: 575–581
Sandberg-Wollheim M, Baird L, Schanfield M *et al* 1984 Association of CSF IgG concentration and immunoglobulin allotype in multiple sclerosis and optic neuritis. *Clin Immunol Immunopathol* **31**: 212–221
Sandberg-Wollheim M, Bynke H, Cronqvist S *et al* 1990 A long term prospective study of optic neuritis: evaluation of risk factors. *Ann Neurol* **27**: 386–393
Sandberg-Wollheim M, Axell T, Hansen BU *et al* 1992 Primary Sjögren's syndrome in patients with multiple sclerosis. *Neurology* **42**: 845–847
Sandberg-Wollheim M, Ciusani E, Salmaggi A, Pociot F 1995 An evaluation of tumour necrosis factor microsatellite alleles in genetic susceptibility to multiple sclerosis. *Mult Scler* **1**: 181–185
Sandberg-Wollheim M, Bever C, Carter J *et al* 2005 Comparative tolerance of IFN beta-1a regimens in patients with relapsing multiple sclerosis. The EVIDENCE study. *J Neurol* **252**: 8–13
Sander M 1898 Hirnrindenbefunde bei multipler Sklerose. *Monatsschr Psychol Neurol* **4**: 429–436
Sanders EACM, Arts RJHM 1986 Paraesthesiae in multiple sclerosis. *J Neurol Sci* **74**: 297–305
Sanders ME, Koski CL, Robbins D *et al* 1986 Activated terminal complement in cerebrospinal fluid in Guillain–Barré syndrome and multiple sclerosis. *J Immunol* **136**: 4456–4459
Sanders V, Conrad AJ, Tourtellotte WW 1993 On classification of post-mortem multiple sclerosis plaques for neuroscientists. *J Neuroimmunol* **46**: 207–216
Sandroni P, Walker C, Starr A 1992 'Fatigue' in patients with multiple sclerosis: motor pathway conduction and event-related potentials. *Arch Neurol* **49**: 517–524
Santiago E, Perez-Mediavilla LA, Lopez-Moratalla N 1998 The role of nitric oxide in the pathogenesis of multiple sclerosis. *J Physiol Biochem* **54**: 229–237
Santos M, Pinto-Basto J, Rio ME *et al* 2003 A whole genome screen for association with multiple sclerosis in Portuguese patients. *J Neuroimmunol* **143**: 112–115
Santos M, Costa M, Rio ME *et al* 2004 Genotypes at the APOE and SCA2 loci do not predict the course of multiple sclerosis in patients of Portugese origin. *Mult Scler* **10**: 153–157
Sarasoja T, Wikstrom J, Paltamaa J 2004 Occurrence of multiple sclerosis in central Finland: a regional and temporal comparison during 30 years. *Acta Neurol Scand* **110**: 331–336
Sarchielli P, Presciutti O, Pelliccioli GP *et al* 1999 Absolute quantification of brain metabolites by proton magnetic resonance spectroscopy in normal appearing white matter of multiple sclerosis patients. *Brain* **122**: 513–522
Sarkari NBS 1968 Involuntary movements in multiple sclerosis. *Br Med J* **2**: 738–740
Sarkari NBS, Bickerstaff ER 1969 Relapses and remissions in brain stem tumours. *Br Med J* **2**: 21–23
Saruhan-Direskeneli G, Weber F, Meinl E *et al* 1993 Human T cell autoimmunity against myelin basic protein: CD4+ cells recognising epitopes of the T cell receptor β chain from a myelin basic protein-specific T cell clone. *Eur J Immunol* **23**: 530–536
Saruhan-Direskeneli G, Esin S, Baykan-Kurt B *et al* 1997 HLA-DR and -DQ associations with multiple sclerosis in Turkey. *Hum Immunol* **55**: 59–65
Sastre-Garriga J, Reverter JC, Font J *et al* 2001 Anticardiolipin antibodies are not a useful screening tool in a nonselected large group of patients with multiple sclerosis. *Ann Neurol* **49**: 408–411
Sastre-Garriga J, Tintore M, Rovira A *et al* 2003 Conversion to multiple sclerosis after a clinically isolated syndrome of the brainstem: cranial magnetic resonance imaging, cerebrospinal fluid and neurophysiological findings. *Mult Scler* **9**: 39–43
Sastre-Garriga J, Tintore M, Rovira A *et al* 2004a Specificity of Barkhof criteria in predicting conversion to multiple sclerosis when applied to clinically isolated brainstem syndromes. *Ann Neurol* **61**: 222–224.
Sastre-Garriga J, Ingle GT, Chard DT *et al* 2004 Grey and white matter atrophy in early clinical stages of primary progressive multiple sclerosis. *Neuroimage* **22**: 353–359
Sastre-Garriga J, Ingle GT, Chard DT *et al* 2005 Grey and white matter volume changes in early primary progressive multiple sclerosis: a longitudinal study. *Brain* **128**: 1454–1460
Sato T, Kamata Y, Irifune M, Nishikawa T 1995 Inhibition of purified (Na+,K+)-ATPase activity from porcine cerebral cortex by NO generating drugs. *Brain Res* **704**: 117–120
Satoh J, Kim SU 1994 Proliferation and differentiation of fetal human oligodendrocytes *in vitro*. *J Neurosci Res* **39**: 260–272
Satoh J, Paty DW, Kim SU 1996 Counteracting effect of IFN-β on IFN-γ-induced proliferation of human astrocytes in culture. *Mult Scler* **1**: 279–287
Satoh JI, Tokumoto H, Kurohara K *et al* 1997 Adult-onset Krabbe disease with homozygous T1853C mutation in the galactocerebrosidase gene: unusual MRI findings of corticospinal tract demyelination. *Neurology* **49**:1203–1204
Sauter MK, Panitch HS, Kristt DA 1991 Myelopathic neurosarcoidosis: diagnostic

value of enhanced MRI. *Neurology* **41**: 150–157
Savettieri G, Daricello B, Giordano D *et al* 1981 The prevalence of multiple sclerosis in Sicily. I. Monreale City. *J Epidemiol Community Health* **35**: 114–117
Savettieri G, Elian M, Giordano D *et al* 1986 A further study on the prevalence of multiple sclerosis in Sicily: Caltanissetta city. *Acta Neurol Scand* **73**: 71–75
Savettieri G, Castiglione MG, D'Arpa A *et al* 1991 Are multiple domicile changes a risk factor for multiple sclerosis? A case-control study. *Neuroepidemiology* **10**: 24–26
Savettieri G, Salemi G, Ragonese P *et al* 1998 Prevalence and incidence of multiple sclerosis in the city of Monreale, Italy. *J Neurol* **245**: 40–43
Savettieri G, Cittadella R, Valentino P *et al* 2002 Lack of an association between estrogen receptor 1 gene polymorphisms and multiple sclerosis in southern Italy in humans. *Neurosci Lett* **327**: 115–118
Savettieri G, Andreoli V, Bonavita S *et al* 2003 Apolipoprotein E genotype does not influence the progression of multiple sclerosis. *J Neurol* **250**: 1094–1098
Savettieri G, Messina D, Andreoli V *et al* 2004 Gender-related effect of clinical and genetic variables on the cognitive impairment in multiple sclerosis. *J Neurol* **251**: 1208–1214
Sawa GM, Paty DW 1979 The use of baclofen in treatment of spasticity in multiple sclerosis. *J Neurol Sci* **6**: 351–356
Sawada M, Hara N, Maeno T 1990 Extracellular tumor necrosis factor induces a decreased K^+ conductance in an identified neuron of *Aplysia kurodai*. *Neurosci Lett* **115**: 219–225
Sawada M, Hara N, Maeno T 1991 Analysis of a decreased Na^+ conductance by tumor necrosis factor in identified neurons of *Aplysia kurodai*. *J Neurosci Res* **28**: 466–473
Sawada M, Ichinose M, Hara N 1995 Nitric oxide induces an increased Na+ conductance in identified neurons of *Aplysia*. *Brain Res* **670**: 248–256
Sawcer SJ, Jones HB, Feakes R *et al* 1996 A genome screen in multiple sclerosis reveals susceptibility loci on chromosome 6p21 and 17q22. *Nature Genet* **13**: 464–468
Sawcer SJ, Jones HB, Judhe D *et al* 1997 Empirical genomewide significance levels established by whole genome simulations. *Genetic Epidemiology* **14**: 223–229
Sawcer SJ, Meranian M, Setakis E *et al* 2002 A whole genome screen for linkage disequilibrium in multiple sclerosis confirms disease associations with regions previously linked to susceptibility. *Brain* **125**: 1337–1347
Sawcer SJ, Maranian M, Singlehurst S *et al* 2004 Enhancing linkage analysis of complex disorders: an evaluation of high-density genotyping. *Hum Mol Genet* **13**: 1943–1949
Scarisbrick IA, Blaber SI, Lucchinetti CF *et al* 2002 Activity of a newly identified serine protease in CNS demyelination. *Brain* **125**: 1283–1296
Scarpini E, Galimberti D, Baron P *et al* 2002 IP-10 and MCP-1 levels in CSF and serum from multiple sclerosis patients with different clinical subtypes of the disease. *J Neurol Sci* **195**: 41–46
Schachter M 1933 Un illustré malade: le poete Henri Heine. *Paris Med* **1 (Suppl)**: 415–417
Schafer DP, Bansal R, Hedstrom KL *et al* 2004 Does paranode formation and maintenance require partitioning of neurofascin 155 into lipid rafts? *J Neurosci* **24**: 3176–3185
Schaltenbrand G 1943 *Die Multiple Sklerose des Menschen*. Leipzig: Thieme
Schapira K 1959 The seasonal incidence of onset and exacerbations in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **22**: 285–286
Schapira K, Poskanzer DC, Millar H 1963 Familial and conjugal multiple sclerosis. *Brain* **86**: 315–332
Schapira K, Poskanzer DC, Newell DJ, Miller H 1966 Marriage, pregnancy and multiple sclerosis. *Brain* **89**: 419–428
Schauf CL, Davis FA 1981 Circulating toxic factors in multiple sclerosis: a perspective. *Adv Neurol* **31**: 267–280
Schauf CL, Smith KJ 1981 Segregation of ionic channels at amphibian nodes of Ranvier. *J Physiol* **320**: 114P–115P
Schaumburg HH, Powers JM, Suzuki K, Raine CS 1974 Adrenoleukodystrophy (sex-linked Schilder disease). *Arch Neurol* **31**: 210–213
Schaumburg HH, Powers JM, Raine CS *et al* 1975 Adrenoleukodystrophy. *Arch Neurol Psychiatry* **32**: 577–591
Schechter SL 1986 Lyme disease associated with optic neuropathy. *Am J Med* **81**: 143–145
Schellekens H, Casadevall N 2004 Immunogenicity of recombinant human proteins: causes and consequences. *J Neurol* **251**: II4–9
Scherb G 1905 Sclérose en plaques fruste ou syndrome cérébelleux de Babinski. *Nouv Iconographie Salpétrière* **18**: 31–35
Scherer SS, Arroyo EJ 2002 Recent progress on the molecular organization of myelinated axons. *J Peripher Nerv Syst* **7**: 1–12
Scherokman BJ, Selhorst JB, Waybright EA *et al* 1985 Improved optic nerve conduction with ingestion of ice water. *Ann Neurol* **17**: 418–419
Schierle G, Hansson O, Leist M *et al* 1999 Caspase inhibition reduces apoptosis and increase survival of nigral transplants. *Nature Med* **5**: 97–100
Schiffenbauer J, Johnson HM, Butfiloski EJ *et al* 1993 Staphylococcal enterotoxins can reactivate experimental allergic encephalomyelitis. *Proc Natl Acad Sci USA* **90**: 8543–8546
Schiffer RB, Caine ED, Bamford KA, Levy S 1983 Depressive episodes in patients with multiple sclerosis. *Am J Psychiatry* **140**: 1498–1500
Schiffer RB, Wineman NM, Weitkamp LR 1986 Association between bipolar affective disorder and multiple sclerosis. *Am J Psychiatry* **143**: 94–95
Schiffer RB, Weitkamp LR, Ford C, Hall WJ 1994 A genetic marker and family history study of the upstate New York multiple sclerosis cluster. *Neurology* **44**: 329–333
Schiffer RB, McDermott MP, Copley C 2001 A multiple sclerosis cluster associated with a small, north-central Illinois community. *Arch Environ Health* **56**: 389–395
Schiffmann R, van der Knaap MA 2004 The latest on leukodystrophies. *Curr Opin Neurol* **17**: 187–192
Schilder P 1912 Zur Kenntnis der sogenannten diffusen Sklerose (über Encephalitis periaxialis diffusa). *Z Neurol Psychiatr* **10**: 1–60
Schimmel MS, Schlesinger Y, Berger I *et al* 2002 Transverse myelitis: unusal sequelae of neonatal group B streptococcus disease. *J Perinatol* **22**: 580–581
Schleper B, Stuerenburg HJ 2001 Copper deficiency-associated myelopathy in a 46-year-old woman. *J Neurol* **248**: 705–706
Schlesinger H 1909 Zür Frage der akuten multiplen Sklerose und der encephalomyelitis disseminata im Kindesalter. *Arbeit Neurologish Inst (Wien)* **17**: 410–432
Schlüsener HJ, Meyermann R 1993 Intercrines in brain pathology: expression of intercrines in a multiple sclerosis and Morbus Creutzfeldt–Jacob lesion. *Acta Neuropathol* **86**: 393–396
Schlüsener HJ, Wekerle H 1985 Autoaggressive T lymphocyte lines recognizing the encephalitogenic region of myelin basic protein: *in vitro* selection from unprimed rat T lymphocyte populations. *J Immunol* **135**: 3128–3133
Schlüsener HJ, Sobel RA, Linington C, Weiner HL 1987 A monoclonal antibody against a myelin oligodendrocyte glycoprotein induces relapses and demyelination in central nervous system autoimmune disease. *J Immunol* **139**: 4016–4021
Schlüter D, Meyer T, Kwok LY *et al* 2002 Phenotype and regulation of persistent intracerebral T cells in murine *Toxoplasma* encephalitis. *J Immunol* **169**: 315–322
Schmidt J, Gold R, Schönrock L *et al* 2000 T-cell apoptosis in situ in experimental autoimmune encephalomyelitis following methylprednisolone pulse therapy. *Brain* **123**: 1431–1441
Schmidt R, Fazekas F, Offenbacher H *et al* 1991 Magnetic resonance imaging white matter lesions and cognitive impairment in hypertensive individuals. *Arch Neurol* **48**: 417–420
Schmidt RT, Lee RH, Spehlemann R 1976 Comparison of dantrolene sodium and diazepam in the treatment of spasticity. *J Neurol Neurosurg Psychiatry* **39**: 350–356
Schmidt S, Hertfelder HJ, von Spiegel T *et al* 1999 Lethal capillary leak syndrome after a single administration of interferon beta-1b. *Neurology* **53**: 220–222
Schmidt S, Barcellos LF, DeSombre K *et al* 2002 Association of polymorphisms in the

apolipoprotein E region with susceptibility to and progression of multiple sclerosis. *Am J Hum Genet* **70**: 708–717
Schmidt S, Passotiropoulos A, Sotgiu S *et al* 2003 Investigation of a genetic variation of a variable number tandem repeat polymorphism of interleukin-6 gene in patients with multiple sclerosis. *J Neurol* **250**: 607–611
Schmied M, Breitschopf H, Gold R *et al* 1993 Apoptosis of T lymphocytes – a mechanism to control inflammation in the brain. *Am J Pathol* **143**: 446–452
Schmierer K, Irlbacher K, Grosse P *et al* 2002 Correlates of disability in multiple sclerosis detected by transcranial magnetic stimulation. *Neurology* **59**: 1218–1224
Schmierer K, Scaravilli F, Altmann DR *et al* 2004 Magnetization transfer ratio and myelin content in *post mortem* multiple sclerosis brain. *Ann Neurol* **56**: 407–415
Schmucker J, Ader M, Brockschnieder D *et al* 2003 erbB3 is dispensable for oligodendrocyte development in vitro and in vivo. *Glia* **44**: 67–75
Schmutzhardt E, Pohl P, Stanek G 1988 *Borrelia burgdorferi* antibodies in patients with relapsing/remitting form and chronic progressive form of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **51**: 1215–1218
Schnadelbach O, Blaschuk OW, Symonds M *et al* 2000 N-cadherin influences migration of oligodendrocytes on astrocyte monolayers. *Mol Cell Neurosci* **15**: 288–302
Schneider C, Gold R, Dalakas MC *et al* 1996 MHC class I mediated cytotoxicity does not induce apoptosis in muscle fibers nor in inflammatory T cells: studies in patients with polymyositis, dermatomyositis and inclusion body myositis. *J Neuropathol Exp Neurol* **55**: 1205–1209
Schneider RD, Ong BH, Moran MJ, Greenhouse AH 1969 Multiple sclerosis in early childhood: case report with notes of frequency. *Clin Pediatr* **8**: 115–118
Schnell L, Fearn S, Schwab ME *et al* 1999 Cytokine-induced acute inflammation in the brain and spinal cord. *J Neuropathol Exp Neurol* **58**: 245–254
Schnider A, Benson FD, Rosner LJ 1993 Callosal disconnection in multiple sclerosis. *Neurology* **43**: 1243–1245
Schob F 1907 Ein Beitrag zür pathologïschen Anatomie der multiplen Sklerose. *Monataschr Psychiat Neurol* **22**: 62–87
Schob F 1923 Über Wurzelfibromatose bei multipler Sklerose. *Z Neurol Psychiatr* **83**: 481–496
Scholl GB, Song H-S, Wray SH 1991 Uhthoff's symptom in optic neuritis: relationship to magnetic resonance imaging and development of multiple sclerosis. *Ann Neurol* **30**: 180–184
Scholz A, Reid G, Vogel W, Bostock H 1993 Ion channels in human axons. *J Neurophysiol* **70**: 1274–1279
Schon F, Hart PE, Hodgson TL *et al* 1999 Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. *Neurology* **53**: 2209–2210
Schon F, Hodgson TL, Mort D, Kennard C 2001 Ocular flutter associated with a localized lesion in the paramedian pontine reticular formation. *Ann Neurol* **50**: 413–416
Schonrock LM, Kuhlmann T, Adler S *et al* 1998 Identification of glial cell proliferation in early multiple sclerosis lesions. *Neuropathol Appl Neurobiol* **24**: 320–330
Schori H, Kipnis J, Yoles E *et al* 2001 Vaccination for protection of retinal ganglion cells against death from glutamate cytotoxicity and ocular hypertension: implications for glaucoma. *Proc Natl Acad Sci USA* **98**: 3398–3403
Schorlemmer HU, Seiler FR 1991 15-deoxyspergualin (15-DOS) for therapy in an animal model of multiple sclerosis (MS): disease modifying activity on acute and chronic relapsing experimental allergic encephalomyelitis (EAE). *Agents Actions* **34**: 156–160
Schrader H, Gotlibsen OB, Skomedal GN 1980 Multiple sclerosis and narcolepsy/cataplexy in a monozygotic twin. *Neurology* **30**: 105–108
Schreiber K, Oyurai AB, Ryder LP *et al* 2002 Disease severity in Danish multiple sclerosis patients evaluated by MRI and three genetic markers (HLA-DRB1*1501, CCR5 deletion mutation, apolipoprotein E). *Mult Scler* **8**: 295–298
Schrijver HM, Crusius JB, Uitehaag BM *et al* 1999 Association of interleukin-1beta and interleukin-1 receptor antagonist genes with disease severity in MS. *Neurology* **52**: 595–599
Schrijver HM, van As J, Crusius JB *et al* 2003 Interleukin (IL)-1 gene polymorphisms: relevance of disease severity associated alleles with IL-1beta and IL-1ra production in multiple sclerosis. *Mediators Inflamm* **12**: 89–94
Schrijver HM, Crusius JB, Garcia-Gonzalez MA *et al* 2004 Gender-related association between the TGFB1+869 polymorphism and multiple sclerosis. *J Interferon Cytokine Res* **24**: 536–542
Schrijver IA, van Meurs M, Melief M-J *et al* 2001 Bacterial peptidoglycan and immune reactivity in the central nervous system in multiple sclerosis. *Brain* **124**: 1544–1554
Schroder R, Zander H, Andreas A, Mauff G 1983 Multiple sclerosis: immunogenetic analyses of sib-pair double case families. II Studies on the association of multiple sclerosis with C2, C4, BF, C3, C6 and GLO polymorphisms. *Immunobiol* **164**: 160–170
Schroth WS, Tenner SM, Rappaport BA, Mani R 1992 Multiple sclerosis as a cause of atrial fibrillation and electrocardiographic changes. *Arch Neurol* **49**: 422–424
Schuele SU, Kellinghaus C, Shook SJ *et al* 2005 Incidence of seizures in patients with multiple sclerosis treated with intrathecal baclofen. *Neurology* **64**: 1086–1087
Schuller E, Govaerts A 1983 First results of immunotherapy with immunoglobulin-γ in multiple sclerosis. *Eur Neurol* **22**: 205–212
Schulz T-J, Parkes A, Mizogouchi E *et al* 1996 Development of $CD4^{-}CD8^{-}$abTCR+NK1.1+ T lymphocytes: thymic selection by self antigen. *J Immunol* **157**: 4379–4389
Schumacher GA, Beebe G, Kibler RF *et al* 1965 Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann NY Acad Sci* **122**: 552–568
Schumacher TNM 2003 T-cell-receptor gene therapy. *Nature Rev Immunol* **2**: 512–519
Schumann EM, Kumpfel T, Bergh FT *et al* 2002 Activity of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: correlations with gadolinium-enhancing lesions and ventricular volume. *Ann Neurol* **51**: 763–767
Schurch B, De Sèze M, Denys P et al 2005 Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo-controlled 6-month study. *J Urol* **174**: 196–200
Schuurman PR, Bosch DA, Bossuyt PM *et al* 2000 A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* **342**: 461–468
Schwab C, McGeer PL 2002 Complement activated C4d immunoreactive oligodendrocytes delineate small cortical plaques in multiple sclerosis. *Exp Neurol* **174**: 81–88
Schwankhaus JD, Patronas N, Dorwart R, Eldridge R, Schlesinger S, McFarland H 1988 Computed tomography and magnetic resonance imaging in a newly described adult-onset leukodystrophy. *Arch Neurol* **45**: 1004–1008
Schwankhaus JD, Katz DA, Eldridge R, Schlesinger S, McFarland H 1994 Clinical and pathological features of an autosomal dominant, adult-onset leukodystrophy simulating chronic progressive multiple sclerosis. *Arch Neurol* **51**: 757–766
Schwankhaus JD, Parisi JE, Gulledge WR *et al* 1995 Hereditary adult-onset Alexander's disease with palatal myoclonus, spastic paraparesis and cerebellar ataxia. *Neurology* **45**: 2226–2271
Schwartz M 2001 Physiological approaches to neuroprotection: boosting of protective autoimmunity. *Survey Ophthalmol* **45**: S256–S260; discussion S273–S276
Schwartz M, Kipnis J 2001 Protective autoimmunity: regulation and prospects for vaccination after brain and spinal cord injuries. *Trends Mol Med* **7**: 252–258
Schwartz M, Moalem G, Leibowitz-Amit R, Cohen IR 1999 Innate and adaptive immune responses can be beneficial for CNS repair. *Trends Neurosci* **22**: 295–299
Schwartzberg C, le Goff P, le Menn C 1981 Complications neuro-ophthalmologique de

lupus erythémateux disséminé. *Semaine Hôpitaux* **57**: 1292–1300
Schwarz JR, Grigat G 1989 Phenytoin and carbamazepine: potential- and frequency-dependent block of Na currents in mammalian myelinated nerve fibers. *Epilepsia* **30**: 286–294
Schwarz JR, Corrette BJ, Mann K, Wietholter H 1991 Changes of ionic channel distribution in myelinated nerve fibres from rats with experimental allergic neuritis. *Neurosci Lett* **122**: 205–209
Schwarz S, Knauth M, Schwab S *et al* 2000 Acute disseminated encephalomyelitis after parenteral therapy with herbal extracts: a report of two cases. *J Neurol Neurosurg Psychiatry* **69**: 516–518
Schwarz S, Mohr A, Knauth M *et al* 2001 Acute disseminated encephalomyelitis: a follow up study of 40 adult patients. *Neurology* **56**: 1313–1318
Schweer D, Jacobsen M, Ziegler A *et al* 2001 No association of three polymorphisms in the alpha-2-macroglobulin and lipoprotein related receptor genes with multiple sclerosis. *J Neuroimmunol* **118**: 300–303
Schwid SR, Bever CT Jr 2001 The cost of delaying treatment in multiple sclerosis: what is lost is not regained. *Neurology* **56**: 1620
Schwid SR, Noseworthy JH 1999 Targeting immunotherapy in multiple sclerosis: a near hit and a clear miss. *Neurology* **53**: 444–445
Schwid SR, Murray TJ 2005 Treating fatigue in patients with MS: one step forward, one step back. *Neurology* **64**: 1111–1112
Schwid SR, Goodman AD, Puzas JE *et al* 1996 Sporadic corticosteroid pulses and osteoporosis in multiple sclerosis. *Arch Neurol* **53**: 753–757
Schwid SR, Goodman AD, Mattson DH 1997a Autoimmune hyperthyroidism in patients with multiple sclerosis treated with interferon beta-1b. *Arch Neurol* **54**: 1169–1190
Schwid SR, Petrie MD, McDermott MP *et al* 1997b Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis. *Neurology* **48**: 817–821
Schwid SR, Petrie MD, Murray R *et al* 2003 A randomized controlled study of the acute and chronic effects of cooling therapy for MS. *Neurology* **60**: 1955–1960
Schwob VS, Clark HB, Agrawal D, Agrawal HC 1985 Electron microscopic immunocytochemical localization of myelin proteolipid protein and myelin basic protein to oligodendrocytes in rat brain during myelination. *J Neurochem* **45**: 559–571
Sciacca FL, Ferr C, Vandenbroeck K *et al* 1999 Relevance of interleukin 1 receptor antagonist intron 2 polymorphism in Italian MS patients. *Neurology* **52**: 1896–1898
Sciacca FL, Ferri C, D'Alfonso S *et al* 2000 Association study of a new polymorphism in the PECAM-1 gene in multiple sclerosis. *J Neuroimmunol* **104**: 174–178
Scolding NJ 2001 New cells from old. *Lancet* **357**: 329–330
Scolding NJ, Compston DAS 1991 Oligodendrocyte susceptibility to injury by specific antibodies. *Immunology* **72**: 127–132
Scolding N, Compston DAS 1995 Growth factors fail to protect rat oligodendrocytes against humoral injury *in vitro*. *Neurosci Lett* **183**: 75–78
Scolding NJ, Morgan BP, Houston A *et al* 1989a Normal rat serum cytotoxicity against syngeneic oligodendrocytes: complement activation and attack in the absence of anti-myelin antibodies. *J Neurol Sci* **89**: 289–300
Scolding NJ, Morgan BP, Houston WAJ *et al* 1989b Vesicular removal by oligodendrocytes of membrane attack complexes formed by complement. *Nature* **339**: 620–622
Scolding N, Jones J, Compston DAS, Morgan BP 1990 Oligodendrocyte susceptibility to injury by T-cell perforin. *Immunology* **70**: 6–10
Scolding NJ, Morgan BP, Campbell AK, Compston DAS 1992 The role of calcium in rat oligodendrocyte injury and repair. *Neurosci Lett* **135**: 95–97
Scolding NJ, Rayner PJ, Sussman J *et al* 1995 A proliferative adult human oligodendrocyte progenitor. *NeuroReport* **6**: 441–445
Scolding NJ, Jayne DRW, Zajicek JP, Meyer PAR, Wriaght EP, Lockwood CM 1997 Cerebral vasculitis – recognition, diagnosis and management. *Q J Med* **90**: 61–73
Scolding NJ, Morgan BP, Compston DAS 1998a The expression of complement regulatory proteins by adult human oligodendrocytes. *J Neuroimmunol* **84**: 69–75
Scolding NJ, Franklin R, Stevens S *et al* 1998b Oligodendrocyte progenitors are present in the normal adult human CNS and in the lesions of multiple sclerosis. *Brain* **121**: 2221–2228
Scott FB, Bradley WE, Timm GW 1973 Treatment of urinary incontinence by an implantable prosthetic sphincter. *Urology* **1**: 252–259
Scott TF 1993 Neurosarcoidosis: progress and clinical aspects. *Neurology* **43**: 8–12
Scott TF, Hess D, Brillman J 1994 Antiphospholipid antibody syndrome mimicking multiple sclerosis clinically and by magnetic resonance imaging. *Arch Int Med* **154**: 917–920
Scott TF, Bhagavatula K, Snyder PJ, Chieffe C 1998 Transverse myelitis: comparison with spinal cord presentations of multiple sclerosis. *Neurology* **50**: 429–433
Scott TF, Schramke CJ, Novero J, Chieffe C 2000 Short-term prognosis in early relapsing–remitting multiple sclerosis. *Neurology* **55**: 689–693
Scotti G, Gerevini S 2001 Diagnosis and differential diagnosis of acute transverse myelopathy: the role of neuroradiological investigations and review of the literature. *Neurol Sci* **22**: S69–S73
Sean Riminton D, Körner H, Strickland DH *et al* 1998 Challenging cytokine redundancy: inflammatory cell movement and clinical course of experimental autoimmune encephalomyelitis are normal in lymphotoxin-deficient, but not tumor necrosis factor-deficient, mice. *J Exp Med* **187**: 1517–1528
Sears TA, Bostock H 1981 Conduction failure in demyelination: is it inevitable? *Adv Neurol* **31**: 357–375
Sears TA, Bostock H, Sheratt M 1978 The pathophysiology of demyelination and its implications for the symptomatic treatment of multiple sclerosis. *Neurology* **28**: 21–26
Seboun E, Robinson MA, Doolittle TH *et al* 1989 A susceptibility locus for multiple sclerosis is linked to the T cell receptor beta chain complex. *Cell* **57**: 1095–1100
Seboun E, Oksenberg JR, Rombos A *et al* 1999 Linkage analysis of candidate myelin genes in familial multiple sclerosis. *Neurogenetics* **2**: 155–162
Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS) Study Group 2001 Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. *Neurology* **56**: 1496–1504
Sedano MJ, Trejo JM, Macarron JL *et al* 2000 Continuous facial myokymia in multiple sclerosis: treatment with botulinum toxin. *Eur Neurol* **43**: 137–140
Seddon B, Zamoyska R 2003 Regulation of peripheral T-cell homeostasis by receptor signalling. *Curr Opin Immunol* **15**: 321–324
Sedgwick JD 1988 Long-term depletion of $CD8^+$ T cells in vivo in the rat: no observed role for $CD8^+$ (cytotoxic/suppressor) cells in the immunoregulation of experimental allergic encephalomyelitis. *Eur J Immunol* **18**: 495–502
Seeldrayers PA, Borenstein S, Gerard J-M, Flament-Durand J 1987 Reversible capsulo-tegmental locked-in state as first manifestation of multiple sclerosis. *J Neurol Sci* **80**: 153–160
Segal BM, Klinman DM, Shevach EM 1997 Microbial products induce autoimmune disease by an IL-2 dependent pathway. *J Immunol* **158**: 5087–5090
Segal BM, Dwyer BK, Shevach EM 1998 An interleukin (IL)-10/IL-12 immunoregulatory circuit controls susceptibility to autoimmune disease. *J Exp Med* **187**: 537–546
Seguin EC 1880 On the coincidence of optic neuritis and subacute transverse myelitis. *J Nerv Mental Dis* **5**: 281–293
Seguin EC, Shaw JC, van Derveer A 1878 A contribution to the pathological anatomy of disseminated cerebro-spinal sclerosis. *J Nerv Mental Dis* **5**: 281–293
Seiffer W 1905 Über psychische, inbesondere Intelligenzstörungen bei multipler Sklerose. *Arch Psychiatr Nervenkr* **40**: 252–303
Seil FJ, Smith ME, Leiman AL, Kelly JM 1975 Myelination inhibiting and neuroelectric blocking factors in experimental allergic encephalomyelitis. *Science* **187**: 951–953
Seil FJ, Leiman AL, Kelly JM 1976 Neuroelectric blocking factors in multiple

sclerosis and normal human sera. *Arch Neurol* **33**: 418–422
Seilhean D, Gansmuller A, Baron-van Evercooren A *et al* 1996 Myelination by transplanted human and mouse central nervous system tissue after long-term cryopreservation. *Acta Neuropathol* **91**: 82–88
Seitelberger F 1960 Histochemistry of demyelinating diseases proper including allergic encephalomyelitis and Pelizaues-Merzbacher's disease. In: Cumings JN (ed.) *Modern Scientific Aspects of Neurology*. London: Arnold, pp. 146–185
Seitelberger F 1967 Autoimmunologic aspects of demyelinating encephalitides. *Nervenarzt* **38**: 525–535
Seitelberger F 1973 Pathology of multiple sclerosis. *Ann Clin Res* **5**: 337–344
Seitelberger F, Jellinger K, Tschabitscher H 1958 Zür Genese der akuten Entmarkungsenzephalitis. *Wien Klin Wochenschr* **70**: 453–459
Selcen D, Anlar B, Renda Y 1996 Multiple sclerosis in childhood: report of 16 cases. *Eur Neurol* **36**: 79–84
Self SG, Longton G, Kopecky KG, Liang KY 1991 On estimating HLA/diseases association with application to a study of aplastic anaemia. *Biometrics* **47**: 53–61
Selhorst JB, Saul RF 1995 Uhthoff and his symptom. *J Neuroophthalmol* **15**: 63–69
Sellebjerg FT, Fredriksen JL, Olssson T 1994 Anti-myelin basic protein and anti-proteolipid protein antibody-secreting cells in the cerebrospinal fluid of patients with acute optic neuritis. *Arch Neurol* **51**: 1032–1036
Sellebjerg F, Christiansen M, Nielsen PM, Frederiksen JL 1998a Cerebrospinal fluid measures of disease activity in patients with multiple sclerosis. *Mult Scler* **4**: 475–479
Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J 1998b Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. *Neurology* **51**: 529–534
Sellebjerg F, Jaliashvili I, Christiansen M, Garred P 1998c Intrathecal activation of the complement system and disability in multiple sclerosis. *J Neurol Sci* **157**: 168–174
Sellebjerg F, Frederiksen JL, Nielsen PM, Olesen J 1999 [Randomized controlled trial of high-dose peroral methylprednisolone in attacks of multiple sclerosis]. *Ugeskrift Laeger* **161**: 6625–6629
Sellebjerg F, Madsen HO, Jensen CV *et al* 2000a CCR5 delta32, matrix metalloproteinase-9 and disease activity in multiple sclerosis. *J Neuroimmunol* **102**: 98–106
Sellebjerg F, Christiansen M, Jensen J, Frederiksen JL 2000b Immunological effects of oral high-dose methylprednisolone in acute optic neuritis and multiple sclerosis. *Eur J Neurol* **7**: 281–289
Sellebjerg F, Giovannoni G, Hand A *et al* 2002 Cerebrospinal fluid levels of nitric oxide metabolites predict response to methylprednisolone treatment in multiple sclerosis and optic neuritis. *J Neuroimmunol* **125**: 198–203
Selmaj K, Raine CS 1988 Tumour necrosis factor mediates myelin and oligodendrocyte damage *in vitro*. *Ann Neurol* **23**: 339–346
Selmaj KW, Raine CS 1995 Experimental autoimmune encephalomyelitis: immunotherapy with anti-tumor necrosis factor antibodies and soluble tumor necrosis factor receptors. *Neurology* **45:** S44–S49
Selmaj K, Farooq M, Norton WT *et al* 1990 Proliferation of astrocytes *in vitro* in response to cytokines: a primary role for tumor necrosis factor. *J Immunol* **144**: 129–135
Selmaj K, Brosnan CF, Raine CS 1991a Colocalization of lymphocytes bearing γδ T-cell receptor and heat shock protein hsp65$^+$ oligodendrocytes in multiple sclerosis. *Proc Natl Acad Sci USA* **88**: 6452–6456
Selmaj K, Raine C, Cannella B, Brosnan C 1991b Identification of lymphotoxin and tumour necrosis factor in multiple sclerosis lesions. *J Clin Invest* **87**: 949–954
Selmaj K, Raine CS, Farooq M *et al* 1991c Cytokine cytotoxicity against oligodendrocytes: apoptosis induced by lymphotoxin. *J Immunol* **147**: 1522–1529
Selmaj K, Brosnan CF, Raine CS 1992 Expression of heat shock protein-65 by oligodendrocytes *in vivo* and *in vitro*: implications for multiple sclerosis. *Neurology* **42**: 795–800
Semana G, Yaouang J, Alizadeh M *et al* 1997 Interleukin-1 receptor antagonist gene in multiple sclerosis. *Lancet* **349**: 476
Semra YK, Seidi OA, Sharief MK 2002 Heightened intrathecal release of axonal cytoskeletal proteins in multiple sclerosis is associated with progressive disease and clinical disability. *J Neuroimmunol* **122**: 132–139
Senaratne MPJ, Carroll D, Warren KG, Kappagoda T 1984 Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **47**: 947–952
Senejoux A, Roulot D, Belin C, Tsakiris L 1996 Myélite aigüe après immunisation contre l'hépatite B par un vaccin recombinant. *Gastroenterol Clin Biol* **20**: 401–402
Sepcic J, Antonelli L, Materljan E, Sepic-Grahovac D 1989 Multiple sclerosis cluster in Gorski Kotar, Croatia, Yugoslavia. In: Battaglia M (ed.) *Multiple Sclerosis Research*. Amsterdam: Elsevier, pp. 165–169
Septien L, Bourgois M, Altaba A *et al* 1991 La sclérose en plaques chez l'enfant. L'impact des troubles de la mémoire. *Arch Fr Pediatr* **48**: 263–265
Serafini B, Rosicarelli B, Magliozzi R, Stigliano E, Aloisi F 2004 Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. *Brain Pathol* **14**: 164–174
Serjeantson SW, Gao X, Hawkins BR *et al* 1992 Novel HLA-DR2 related haplotypes in Hong Kong Chinese implicate the DQB1.0602 allele in susceptibility to multiple sclerosis. *Eur J Immunol* **19**: 11–19
Sesboue R, Daveau M, Degos J *et al* 1985 IgG (Gm) allotypes and multiple sclerosis in a French population: phenotype distribution and quantitative abnormalities in CSF with respect to sex, disease severity and presence of intrathecal antibodies. *Clin Immunol Immunopathol* **37**: 143–153
Setakis E 2003 Statistical analysis of the GAMES studies. *J Neuroimmunol* **143**: 47–52
Setzu A, ffrench-Constant C, Franklin RJ 2004 CNS axons retain their competence for myelination throughout life. *Glia* **45**: 307–311
Shaby JA 1958 Multiple sclerosis in Iraq. *Wein Z Nervenheilk* **15**: 267–283
Shafit-Zagardo B, Kress Y, Zhao ML, Lee SC 1999 A novel microtubule-associated protein-2 expressed in oligodendrocytes in multiple sclerosis lesions. *J Neurochem* **73**: 2531–2537
Shah BS, Stevens EB, Gonzalez MI *et al* 2000 beta3, a novel auxiliary subunit for the voltage-gated sodium channel, is expressed preferentially in sensory neurons and is upregulated in the chronic constriction injury model of neuropathic pain. *Eur J Neurosci* **12**: 3985–3990
Shahrokhi F, Chiappa KH, Young RR 1978 Pattern shift visual evoked responses. *Arch Neurol* **35**: 65–71
Shakespeare DT, Boggild M, Young C 2003 Anti-spasticity agents for multiple sclerosis (Cochrane Review). *Cochrane Library* **3**: update software
Shakir RA, Sulaiman RA, Rudman M 1990 Neurological presentation of neuro-Behçet's syndrome: clinical categories. *Eur Neurol* **30**: 249–253
Sham P, Bader JS, Craig I *et al* 2002 DNA pooling: a tool for large-scale association studies. *Nature Rev Genet* **3**: 862–871
Shao Y, McCarthy KD 1994 Plasticity of astrocytes. *Glia* **11**: 147–155
Shapiro S, Galboiz Y, Lahat N *et al* 2003 The 'immunological-synapse' at its APC side in relapsing and secondary-progressive multiple sclerosis: modulation by interferon-beta. *J Neuroimmunol* **144**: 116–124
Sharief MK Hentges R 1991 Association between tumor necrosis factor-alpha and disease progression in patients with multiple sclerosis. *N Engl J Med* **325**: 467–472
Sharief MK, Thompson EJ 1992 *In vivo* relationship of tumor necrosis factor-alpha to blood brain barrier damage in patients with active multiple sclerosis. *J Neuroimmunol* **38**: 27–33
Sharief MK, Thompson EJ 1993 Correlation of interleukin-2 and soluble interleukin-2 receptor with clinical activity of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **56**: 169–174
Sharief MK, Noori MA, Ciardi M, Cirelli A, Thompson EJ 1993 Increased levels of

circulating ICAM-1 in serum and cerebrospinal fluid of patients with active multiple sclerosis: correlation with TNF-alpha and blood–brain barrier damage. *J Neuroimmunol* **43**: 15–21
Sharpe G, Price SE, Last A, Thompson RJ 1995 Multiple sclerosis in island populations – prevalence in the Bailiwicks of Guernsey and Jersey. *J Neurol Neurosurg Psychiatry* **58**: 22–26
Sharpe JA 2003 Gaze disorders. In: Noseworthy JH (ed.) *Neurological Therapeutics: Principles and Practice*. London: Martin Dunitz, pp.1799–1816
Sharpe JA, Sanders MD 1975 Atrophy of myelinated nerve fibres in the retina in optic neuritis. *Br J Ophthalmol* **59**: 229–232
Sharpe JA, Hoyt WF, Rosenberg MA 1975 Convergence evoked nystagmus: congenital and acquired. *Arch Neurol* **32**: 191–194
Sharrack B, Hughes RAC 1999 The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis. *Mult Scler* **5**: 223–233
Sharrack B, Hughes RAC, Soudain S, Dunn G 1999 The psychometric properties of clinical rating scales used in multiple sclerosis. *Brain* **122**: 141–159
Sharrack B, Hughes RA, Morris RW *et al* 2000 The effect of oral and intravenous methylprednisolone treatment on subsequent relapse rate in multiple sclerosis. *J Neurolog Sci* **173**: 73–77
Shaw AS 2001 FERMing up the synapse. *Immunity* **15**: 683–686
Shaw CE, Dunbar PR, Macaulay HA, Neale TJ 1995 Measurement of immune markers in the serum and cerebrospinal fluid of multiple sclerosis patients during clinical remission. *J Neurol* **242**: 53–58
Shaw CE, Milner RM, Compston DAS, ffrench Constant C 1996 Integrin expression during axo-glial interactions: a developmental comparison of oligodendrocytes and Schwann cells. *J Neurosci* **16**: 1163–1172
Shaw CM, Alvord EC 1987 Multiple sclerosis beginning in infancy. *J Child Neurol* **2**: 252–256
Shaw FE, Graham DJ, Guess HA, Milstein JB 1988 Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. *Am J Epidemiol* **127**: 337–352
Shaw PJ, Smith NM, Ince PG, Bates D 1987 Chronic periphlebitis retinae in multiple sclerosis: a histological study. *J Neurol Sci* **77**: 147–152
Sheean GL, Murray NMF, Rothwell JC *et al* 1997 An electrophysiological study of the mechansism of fatigue in multiple sclerosis. *Brain* **120**: 299–315
Sheffner JM, Mackin GA, Dawson DM 1992 Lower motor dysfunction in patients with multiple sclerosis. *Muscle Nerve* **15**: 1265–1270
Sheikh KA, Sun J, Liu Y *et al* 1999 Mice lacking complex gangliosides develop Wallerian degeneration and myelination defects. *Proc Natl Acad Sci USA* **96**: 7532–7537
Shepherd DI 1979 Clinical features of multiple sclerosis in north-east Scotland. *Acta Neurol Scand* **60**: 218–230
Shepherd DI, Downie AW 1978 Prevalence of multiple sclerosis in North East Scotland. *Br Med J* **2**: 314–316
Shepherd DI, Downie AW 1980 A further prevalence study of multiple sclerosis in North East Scotland. *J Neurol Neurosurg Psychiatry* **43**: 310–315
Shepherd DI, Summers A 1996 The prevalence of multiple sclerosis in Rochdale. *J Neurol Neurosurg Psychiatry* **61**: 415–417
Sheremata WA, Poskanzer DC, Withum DG *et al* 1985 Unusual occurrence on a tropical island of multiple sclerosis (letter). *Lancet* **2**: 618
Sherratt RM, Bostock H, Sears TA 1980 Effects of 4-aminopyridine on normal and demyelinated mammalian nerve fibres. *Nature* **283**: 570–572
Sherrington CS 1906 *The Integrative Action of the Nervous System*. New York: Charles Scribner's Sons
Sherritt MA, Oksensberg JR, Kerlero de Rosbo N, Bernard CCA 1992 Influence of HLA-DR2, HLA-DPw4 and the T cell receptor alpha chain genes on the susceptibility to multiple sclerosis. *Int Immunol* **4**: 177–181
Sherwin AL 1957 Multiple sclerosis in historical perspective. *McGill Med J* **26**: 39–48
Shevell MI, Bradley BK 1994 The 'Schaltenbrand experiment', Wurzburg, 1940: scientific, historical, and ethical perspectives. *Neurology* **44**: 350–356
Shi Y, Lie DC, Taupin P *et al* 2004 Expression and function of orphan nuclear receptor TLX in adult neural stem cells. *Nature* **427**: 78–83
Shibasaki H, Kuroiwa Y 1974 Painful tonic seizure in multiple sclerosis. *Arch Neurol* **30**: 437–451
Shibasaki H, McDonald WI, Kuroiwa Y 1981 Racial modification of clinical picture of multiple sclerosis: comparison between British and Japanese patients. *J Neurol Sci* **49**: 253–271
Shields GS, Castillo M 2002 Myelitis caused by *Cladophialophora bantiana*. *Am J Roentgenol* **179**: 278–279
Shimizu T, Kagawa T, Wada T *et al* 2005 Wnt signaling controls the timing of oligodendrocyte development in the spinal cord. *Dev Biol* **282**: 397–410
Shimizu Y, Newman W, Tanaka Y, Shaw S 1992 Lymphocyte interaction with endothelial cells. *Immunol Today* **13**: 106–112
Shimonkevitz R, Colburn C, Burnham JA *et al* 1993 Clonal expansion of activated γ/δ T cells in recent-onset multiple sclerosis. *Proc Natl Acad Sci USA* **90**: 923–927
Shin T, Kim S, Moon C *et al* 2000 Aminoguanidine-induced amelioration of autoimmune encephalomyelitis is mediated by reduced expression of inducible nitric oxide synthase in the spinal cord. *Immunol Invest* **29**: 233–241
Shinar Y, Pras E, Siev-Ner I *et al* 1998 Analysis of allelic association between D6S461 marker and multiple sclerosis in Ashkenazi and Iraqi Jewish patients. *J Mol Neurosci* **11**: 265–269
Shinar Y, Livneh A, Villa Y *et al* 2003 Common mutations in the familial Mediterranean fever gene associated with rapid progression to disability in non-Ashkenazi Jewish multiple sclerosis patients. *Genes Immun* **4**: 197–203
Shinder V, Amir R, Devor M 1998 Cross-excitation in dorsal root ganglia does not depend on close cell-to-cell apposition. *NeuroReport* **9**: 3997–4000
Shintaku M, Hirano A, Llena JF 1988 Increased diameter of demyelinated axons in chronic multiple sclerosis of the spinal cord. *Neuropathol Appl Neurobiol* **14**: 505–510
Shiraishi K, Higuchi Y, Ozawa K 2004 Dystonia in a 13 year old boy with secondary progressive multiple sclerosis. *Brain Dev* **26**: 539–541
Shirazi Y, Rus HG, Macklin WB, Shin ML 1993 Enhanced degradation of messenger RNA encoding myelin proteins by terminal complement complexes in oligodendrocytes. *J Immunol* **150**: 4581–4590
Shores EW, Van Ewijk W, Singer A 1991 Disorganization and restoration of thymic medullary epithelial cells in T cell receptor-negative SCID mice: evidence that receptor-bearing lymphocytes influence maturation of the thymic microenvironment. *Eur J Immunol* **21**: 1657–1661
Shortman K, LiuY-J 2002 Mouse and human dendritic cell subtypes. *Nature Rev Immunol* **2**: 151–161
Shrager P 1977 Slow sodium inactivation in nerve after exposure to sulhydryl blocking reagents. *J Gen Physiol* **69**: 183–202
Shrager P 1993 Axonal coding of action potentials in demyelinated nerve fibers. *Brain Res* **619**: 278–290
Shrager P, Rubinstein CT 1990 Optical measurement of conduction in single demyelinated axons. *J Gen Physiol* **95**: 867–890
Shrager P, Custer AW, Kazarinova K *et al* 1998 Nerve conduction block by nitric oxide that is mediated by the axonal environment. *J Neurophysiol* **79**: 529–536
Sibley JT, Olszynski WP, De Coteau WE, Sundaram MB 1992 The incidence and prognosis of central nervous system disease in systemic lupus erythematosus. *J Rheumatol* **19**: 47–52
Sibley WA, Foley J 1965a Seasonal variation in multiple sclerosis and retrobulbar neuritis in Northeastern Ohio. *Trans Am Neurol Assoc* **90**: 295–297
Sibley WA, Foley JM 1965b Infection and immunization in multiple sclerosis. *Ann NY Acad Sci* **122**: 457–466
Sibley WA, Bamford CR, Laguna JF 1976 Influenza vaccination in patients with multiple sclerosis. *J Am Med Assoc* **236**: 1965–1966

Sibley WA, Bamford CR, Clark K 1984 Triggering factors in multiple sclerosis. In: Poser CM (ed.) *The Diagnosis of Multiple Sclerosis*. New York: Thieme-Stratton, pp. 14–24

Sibley, WA, Bamford CR, Clark K 1985 Clinical viral infections and multiple sclerosis. *Lancet* **i**: 1313–1315

Sibley WA, Bamford CR, Clark K *et al* 1991 A prospective study of physical trauma and multiple sclerosis. *J Neurol Neurosurg Psychiatry* **54**: 584–589

Sichel J 1837 *Traité de l'Ophthalmie, la cataracte et l'amaurose*. Paris: Baillière

Sichel J 1852–1859 *Iconographie ophthalmologique ou description avec figures coloriées des maladies de l'organe de la vue comprenant l'anatomie pathologique, le pathologie et le therapeutique medico-chirurgicales*. Texte et atlas. Paris: Baillière

Sicotte NL, Liva SM, Klutch R *et al* 2002 Treatment of multiple sclerosis with the pregnancy hormone estriol. *Ann Neurol* **52**: 421–428

Siegal FP, Kadowaki N, Shodell M *et al* 1999 The nature of the principal type 1 interferon producing cells in human blood. *Science* **284**: 1835–1837

Siemerling E 1924 Multiple Sklerose (Pathogenese, Aetiologie, Therapie). *Klin Woschenschr* **3**: 609–612

Siemerling E, Raecke J 1911 Zür pathologisdien Anatomie und Pathogenense der multiple on Sklerose. *Arch Psychiatr Nervenkr* **48**: 824

Siemerling E, Raecke E 1914 Beitrag zur Klinik und Pathologie der multiplen Sklerose mit besonderer Berücksichtigung ihrer Pathogenese. *Arch Psychiatr Nervenkr* **53**: 385–564

Siemkowicz E 1976 Multiple sclerosis and surgery. *Anaesthesia* **31**: 1211–1216

Silber E, Semra YK, Gregson NA, Sharief MK 2002 Patients with progressive multiple sclerosis have elevated antibodies to neurofilament subunit. *Neurology* **58**: 1372–1381

Silber MH, Willcox PA, Bowen RM, Unger A 1990 Neuromyelitis optica (Devic's syndrome) and pulmonary tuberculosis. *Neurology* **40**: 934–938

Silberberg, DH, Stuart, WH, van den Noort, S, Therapeutics Technology Assessment Subcommittee of the American Academy of Neurology, The Multiple Sclerosis Council for Clinical Practice Guidelines 2002 Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the Multiple Sclerosis Council for Clinical Practice Guidelines. *Neurology* **58**: 169–178

Silfverskiöld BP 1947 Retinal periphlebitis with paraplegia. *Arch Neurol Psychiatry* **57**: 351–357

Siller MH 1989 Syphilitic myelopathy. *Genitourin Med* **65**: 338–341

Silver NC, Good CD, Barker GJ *et al* 1997 Sensitivity of contrast enhanced MRI in multiple sclerosis: effective gadolinium dose, magnetisation transfer contrast and delayed imaging. *Brain* **120**: 1149–1161

Silver NC, Good CD, Sormani MP *et al* 2001 A modified protocol to improve the detection of enhancing brain and spinal cord lesions in multiple sclerosis. *J Neurol* **248**: 215–224

Silverman N, Maniatis T 2001 NF-kappaB signaling pathways in mammalian and insect innate immunity. *Genes Dev* **15**: 2321–2342

Silversides JA, Heggarty SV, McDonnell GV *et al* 2004 Influence of CCR5 δ32 polymorphism on multiple sclerosis susceptibility and disease course. *Mult Scler* **10**: 149–152

Sim FJ, Zhao C, Li WW *et al* 2002a Expression of the POU-domain transcription factors SCIP/Oct-6 and Brn-2 is associated with Schwann cell but not oligodendrocyte remyelination in the CNS. *Mol Cell Neurosci* **20**: 669–682

Sim FJ, Zhao C, Penderis J, Franklin RJ 2002b The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. *J Neurosci* **22**: 2451–2459

Simeon-Aznar CP, Tolosa-Vilella C, Cuenca-Luque R *et al* 1992 Transverse myelitis in systemic lupus erythematosus: two cases with magnetic resonance imaging. *Br J Rheumatol* **31**: 555–558

Simmons ML, Frondoza CG, Coyle JT 1991 Immunocytochemical localization of N-acetyl-aspartate with monoclonal antibodies. *Neuroscience* **45**: 37–45

Simmons RD, Willenborg DO 1990 Direct injection of cytokine into the spinal cord causes autoimmune encephalomyelitis-like inflammation. *J Neurol Sci* **100**: 37–42

Simmons RD, Bernard CC, Singer G, Carnegie PR 1982 Experimental autoimmune encephalomyelitis: an anatomically-based explanation of clinical progression in rodents. *J Neuroimmunol* **3**: 307–318

Simmons RD, Hall CA, Gleeson P *et al* 2001 Prevalence survey of multiple sclerosis in the Australian Capital Territory. *Intern Med J* **31**: 161–167

Simon JH, Jacobs LD, Campion M *et al* 1997 Magnetic resonance studies of intramuscular interferon β-1a for relapsing multiple sclerosis. *Ann Neurol* **43**: 79–87

Simon JH, Jacobs L, Kinkel RP 2001 Transcallosal bands: a sign of neuronal tract degeneration in early MS? *Neurology* **57**: 1888–1890

Simon RP, Gean-Marton AD, Sander JE 1991 Medullary lesion inducing pulmonary edema: a magnetic resonance imaging study. *Ann Neurol* **30**: 727–730

Simone IL, Carrara D, Tortorella C *et al* 2002 Course and prognosis in early-onset MS: comparison with adult onset forms. *Neurology* **59**: 1922–1928

Simpson CA, Vejjajiva A, Caspary EA, Miller H 1965 ABO blood groups in multiple sclerosis. *Lancet* **i**: 1366–1367

Simpson JE, Newcombe J, Cuzner ML, Woodroofe MN 1998 Expression of monocyte chemoattractant protein-1 and other beta-chemokines by resident glia and inflammatory cells in multiple sclerosis lesions. *J Neuroimmunol* **84**: 238–249

Simpson JE, Rezaie P, Newcombe J *et al* 2000a Expression of the beta-chemokine receptors CCR2, CCR3 and CCR5 in multiple sclerosis central nervous system tissue. *J Neuroimmunol* **108**: 192–200

Simpson JE, Newcombe J, Cuzner ML, Woodroofe MN 2000b Expression of the interferon-gamma-inducible chemokines IP-10 and Mig and their receptor, CXCR3, in multiple sclerosis lesions. *Neuropathol Appl Neurobiol* **26**: 133–142

Sims TJ, Gilmore SA, Waxman SG 1991 Radial glia give rise to perinodal processes. *Brain Res* **549**: 25–35

Sinclair C, Mirakhur M, Kirk J *et al* 2005 Up-regulation of osteopontin and alphaBeta.crystalline in the normal-appearing white matter of multiple sclerosis: an immunohistochemical study utilizing tissue microarrays. *Neuropath Appl Neurobiol* **31**: 292–303

Sindern E, Haas J, Stark E, Wurster U 1992 Early onset MS under the age of 16: clinical and paraclinical features. *Acta Neurol Scand* **86**: 280–284

Sindic CJ, Monteyne P, Laterre EC 1994 The intrathecal synthesis of virus-specific oligoclonal IgG in multiple sclerosis. *J Neuroimmunol* **54**: 75–80

Singer M, Yakovlev PI 1954 *The Human Brain in Saggital Section*. Springfield, IL: C.C. Thomas

Singh AK, Wilson MT, Hong S *et al* 2001 Natural killer T cell activation protects mice against experimental autoimmune encephalomyelitis. *J Exp Med* **194**: 1801–1811

Singh S, Alexander M, Korah IP 1999 Acute disseminated encephalomyelitis: MR imaging features. *Am J Roentgenol* **172**: 1101–1107

Singh VK, Mehrotra S, Narayan P *et al* 2000 Modulation of autoimmune diseases by nitric oxide. *Immunol Res* **22**: 1–19

Singhal BS 1985 Multiple sclerosis – Indian experience. *Ann Acad Med Singapore* **14**: 32–36

Singhal BS, Wadia NH 1975 Profile of multiple sclerosis in the Bombay region on the basis of critical clinical appraisal. *J Neurol Sci* **26**: 259–270

Sinha AA, Bell RB, Steinman L, McDevitt HO 1991 Oligonucleotide dot-blot analysis of HLA-DQbeta alleles associated with multiple sclerosis. *J Neuroimmunol* **32**: 61–65

Sipe JC, Knobler RL, Braheny SL *et al* 1984 A neurologic rating scale (NRS) for use in multiple sclerosis. *Neurology* **34**: 1368–1372

Sipe JC, Romine JS, Kotziol JA *et al* 1994 Cladribine in treatment of chronic progressive multiple sclerosis. *Lancet* **344**: 9–13

Sipski ML, Rosen RC, Alexander CJ, Hamer RM 2000 Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. *Urology* **55**: 812–815

Sironi A, Mamoli A, d'Alessandro G *et al* 1991 Frequency of multiple sclerosis in Valle d'Aosta, 1971–1985. *Neuroepidemiology* **10**: 66–69

Siva A, Radhakrishnan K, Kurland LT *et al* 1993 Trauma and multiple sclerosis: a population based cohort study from Olmsted County, Minnesota. *Neurology* **43**: 1878–1882

Siva A, Kantarci OH, Saip S *et al* 2001 Behcet's disease: diagnostic and prognostic aspects of neurological involvement. *J Neurol* **248**: 95–103

Sivasankaran R, Pei J, Wang KC *et al* 2004 PKC mediates inhibitory effects of myelin and chondroitin sulfate proteoglycans on axonal regeneration. *Nat Neurosci* **7**: 261–268

Skegg DCG, Corwin PA, Craven RS *et al* 1987 Occurrence of multiple sclerosis at the north and south of New Zealand. *J Neurol Neurosurg Psychiatry* **50**: 134–139

Skinner PJ, Haase AT 2002 *In situ* tetramer staining. *J Immunol Meth* **268**: 29–34

Skoff R, Price D, Stocks A 1976 Electron microscope autoradiographic studies of gliogenesis in rat optic nerve. I. Cell proliferation. *J Comp Neurol* **169**: 291–312

Skoog B, Runmarker B, Andersen O 2004 A 37–50 year follow-up of the Gothenburg multiple sclerosis cohort. *Mult Scler 10* **(Suppl)**: S156

Skundric DS, Huston K, Shaw M *et al* 1994 Experimental allergic encephalomyelitis: T cell trafficking to the central nervous system in a resistant Thy-1 congenic mouse strain. *Lab Invest* **71**: 671–679

Slamovits TL, Rosen CE, Cheny KP, Striph GG 1991 Visual recovery in patients with optic neuritis and visual loss to no light perception. *Am J Ophthalmol* **111**: 209–214

Sleeper AA, Cummins TR, Dib-Hajj SD *et al* 2000 Changes in expression of two tetrodotoxin-resistant sodium channels and their currents in dorsal root ganglion neurons after sciatic nerve injury but not rhizotomy. *J Neurosci* **20**: 7279–7289

Sliwa JA, Bell HK, Mason KD *et al* 1996 Upper urinary tract abnormalities in multiple sclerosis patients with urinary symptoms. *Arch Phys Med Rehab* **77**: 247–251

Sloan JB, Berk M, Gebel HM, Fretzin DF 1987 Multiple sclerosis and systemic lupus erythematosus: occurrence in two generations of the same family. *Arch Int Med* **147**: 1317–1320

Sloka JS, Pryse-Phillips WE, Stefanelli M 2005a Incidence and prevalence of multiple sclerosis in Newfoundland and Labrador. *Can J Neurol Sci* **32**: 37–42

Sloka JS, Pryse-Phillips WE, Stefanelli M 2005b Multiple sclerosis in Newfoundland and Labrador – a model for disease prevalence. *Can J Neurol Sci* **32**: 43–49

Small DG 1976 Peripherally evoked spinal cord potentials in neurological diagnosis. In: Nicholson JP (ed.) *Scientific Aids in Hospital Diagnosis*. New York: Plenum Press, pp. 155–163

Small DG, Matthews WB, Small M 1978 The cervical somatosensory evoked potential in the diagnosis of multiple sclerosis. *J Neurol Sci* **35**: 211–224

Small RK, Riddle P, Noble M 1987 Evidence for migration of oligodendrocyte-type 2 astrocyte progenitor cells into the developing rat optic nerve. *Nature* **328**: 155–157

Smeltzer SC, Utell MJ, Rudick RA, Herndon RM 1988 Pulmonary function and dysfunction in multiple sclerosis. *Arch Neurol* **45**: 1245–1249

Smith AJF, Jackson MW, Neufing P *et al* 2004 A functional autoantibody in narcolepsy. *Lancet* **364**: 2122–2124

Smith CP, Nishiguchi J, O'Leary M *et al* 2005 Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. *J Urol* **65**: 37–41

Smith CR, Scheinberg L 1990 Coincidence of myoclonus and multiple sclerosis: dramatic response to clonazepam. *Neurology* **40**: 1633

Smith CR, LaRocca NG, Giesser BS, Scheinberg LA 1991 High-dose oral baclofen: experience in patients with multiple sclerosis. *Neurology* **41**: 1829–1831

Smith CR, Birnbaum G, Carter JL, Greenstein J, Lublin FD, the US Tizanidine Study Group 1994 Tizanidine treatment of spasticity caused by multiple sclerosis. *Neurology* **44 (Suppl 9)**: S34–S43

Smith DR, Balashov KE, Hafler DA *et al* 1997 Immune deviation following pulse cyclophosphamide/methylprednisolone treatment of multiple sclerosis: increased interleukin-4 production and associated eosinophilia. *Ann Neurol* **42**: 313–318

Smith HB, Espir MLE, Whitty CWM *et al* 1957 Abnormal immunological reaction in disseminated sclerosis: a preliminary report. *J Neurol Neurosurg Psychiatry* **20**: 1–10

Smith KJ 1994 Conduction properties of central demyelinated and remyelinated axons, and their relation to symptom production in demyelinating disorders. *Eye* **8**: 224–237

Smith KJ, Hall SM 1980 Nerve conduction during peripheral demyelination and remyelination. *J Neurol Sci* **48**: 201–219

Smith KJ, Hall SM 2001 Factors directly affecting impulse transmission in inflammatory demyelinating disease: recent advances in our understanding. *Curr Opin Neurol* **14**: 289–298

Smith KJ, Lassmann H 2002 The role of nitric oxide in multiple sclerosis. *Lancet Neurol* **1**: 232–241

Smith KJ, McDonald WI 1980 Spontaneous and mechanically evoked activity due to central demyelinating lesion. *Nature* **286**: 154–155

Smith KJ, McDonald WI 1982 Spontaneous and evoked electrical discharges from a central demyelinating lesion. *J Neurol Sci* **55**: 39–47

Smith KJ, McDonald WI 1999 The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. *Phil Trans R Soc Lond* **354**: 1649–1673

Smith KJ, Schauf CL 1981a Effects of gallamine triethiodide on membrane currents in amphibian and mammalian peripheral nerve. *J Pharmacol Exp Ther* **217**: 719–726

Smith KJ, Schauf CL 1981b Gallamine triethiodide (flaxedil): tetraethylammonium- and pancuronium-like effects in myelinated nerve fibers. *Science* **212**: 1170–1172

Smith KJ, Schauf CL 1981c Size-dependent variation of nodal properties in myelinated nerve. *Nature* **293**: 297–299

Smith KJ, Blakemore WF, McDonald WI 1979 Central remyelination restores secure conduction. *Nature* **280**: 395–396

Smith KJ, Blakemore WF, McDonald WI 1981 The restoration of conduction by central remyelination. *Brain* **104**: 383–404

Smith KJ, Bostock H, Hall SM 1982 Saltatory conduction precedes remyelination in axons demyelinated with lysophosphatidylcholine. *J Neurol Sci* **54**: 13–31

Smith KJ, Felts PA, Baker TA 1994 Conduction properties of glial-ensheathed and sparsely ensheathed central demyelinated axons. *Ann Neurol* **36**: 287

Smith KJ, Felts PA, Kapoor R 1997 Axonal hyperexcitability: mechanisms and role in symptom production in demyelinating diseases. *Neuroscientist* **3**: 237–246

Smith KJ, Pyrdol J, Gauthier L *et al* 1998 Crystal structure of HLA-DR2 (DRA*0101, DRB*1501) complexed with a peptide from human myelin basic protein. *J Exp Med* **188**: 1511–1520

Smith KJ, Kapoor R, Felts PA 1999 Demyelination: the role of reactive oxygen and nitrogen species. *Brain Pathol* **9**: 69–92

Smith KJ, Felts PA, John GR 2000 Effects of 4-aminopyridine on demyelinated axons, synapses and muscle tension. *Brain* **123**: 171–184

Smith KJ, Kapoor R, Hall SM, Davies M 2001a Electrically active axons degenerate when exposed to nitric oxide. *Ann Neurol* **49**: 470–476

Smith KJ, Kapoor R, Hall SM, Davies M 2001b Partial sodium channel blockade protects axons from degeneration caused by the combination of impulse activity and exposure to nitric oxide. *Soc Neurosci Meeting Abstr* 103.12

Smith MB, Brar SP, Nelson LM, Franklin GM 1992 Baclofen effect on quadriceps strength in multiple sclerosis. *Arch Phys Med Rehab* **73**: 237–240

Smith ME, Stone LA, Alpert PS *et al* 1993 Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions. *Ann Neurol* **33**: 480–489

Smith ME, Eller NL, McFarland HF *et al* 1999 Age dependence of clinical and pathological manifestations of autoimmune

demyelination: implications for multiple sclerosis. *Am J Pathol* **155**: 1147–1161
Smith MW, Patterson N, Lautenberger JA 2004 A high-density admixture map for disease gene discovery in african americans. *Am J Hum Genet* **74**: 1001–1013
Smith PF 2002 Cannabinoids in the treatment of pain and spasticity in multiple sclerosis. *Curr Opin Invest Drugs* **3**: 859–864
Smith PM, Blakemore WF 2000 Porcine neural progenitors require commitment to the oligodendrocyte lineage prior to transplantation in order to achieve significant remyelination of demyelinated lesions in the adult CNS. *Eur J Neurosci* **12**: 2414–2424
Smith PM, Franklin RJM 2001 The effect of immunosuppressive protocols on spontaneous CNS remyelination following toxin-induced demyelination. *J Neuroimmunol* **119**: 261–268
Smith S, DeStefano N, Jenkinson M, Matthews P 2001 Normalised accurate measurement of longitudinal brain change. *J Comput Assist Tomog* **25**: 466–475
Smith SL, Otis TS 2003 Persistent changes in spontaneous firing of Purkinje neurons triggered by the nitric oxide signaling cascade. *J Neurosci* **23**: 367–372
Smith T, Cuzner ML 1994 Neuroendocrine-immune interactions in homeostasis and autoimmunity. *Neuropathol Appl Neurobiol* **20**: 413–422
Smith T, Zeeberg I, Sjo O 1986 Evoked potentials in multiple sclerosis before and after high-dose methylprednisolone infusion. *Eur Neurol* **25**: 67–73
Smith T, Schmied M, Hewson AK, Lassmann H, Cuzner ML 1996 Apoptosis of T cells and macrophages in the central nervous system of intact and adrenalectomized Lewis rats during experimental allergic encephalomyelitis. *J Autoimmunity* **9**: 167–174
Smith T, Groom A, Zhu B, Turski L 2000 Autoimmune encephalomyelitis ameliorated by AMPA antagonists. *Nature Med* **6**: 62–66
Snider BJ, Choi J, Turetsky DM *et al* 2000 Nitric oxide reduces Ca2+ and Zn2+ influx through voltage-gated Ca2+ channels and reduces Zn2+ neurotoxicity. *Neuroscience* **100**: 651–661
Snow BJ, Tsui JKC, Bhatt MH, Varelas M, Hashimoto SA, Calne DB 1990 Treatment of spasticity with Botulinum toxin: a double-blind study. *Ann Neurol* **28**: 512–515
Sobel RA 2001 The extracellular matrix in multiple sclerosis: an update. *Braz J Med Biol Res* **34**: 603–609
Sobel RA, Ames MB 1988 Major histocompatibility complex molecule expression in the human central nervous system: immunohistochemical analysis of 40 patients. *J Neuropath Exp Neurol* **47**: 19–28
Sobel RA, Mitchell ME 1989 Fibronectin in multiple sclerosis lesions. *Am J Pathol* **135**: 161–168
Sobel RA, Hafler DA, Castro EE *et al* 1988 The 2H4 (CD45R) antigen is selectively decreased in multiple sclerosis lesions. *J Immunol* **140**: 2210–2214
Sobel RA, Mitchell ME, Fondren G 1990 Intercellular adhesion molecule-1 (ICAM-1) in cellular immune reactions in the human central nervous system. *Am J Pathol* **136**: 1309–1316
Söderström M, Lindqvist M, Hillert J *et al* 1994a Optic neuritis: findings on MRI, CSF examination and HLA class II typing in 60 patients and results of short term follow up. *J Neurol* **241**: 391–397
Söderström M, Link H, Sun J-B *et al* 1994b Autoimmune T cell repertoire in optic neuritis and multiple sclerosis: T cells recognizing multiple myelin proteins are accumulated in cerebrospinal fluid. *J Neurol Neurosurg Psychiatry* **57**: 544–551
Söderström M, Hillert J, Link J *et al* 1995 Expression of IFN-γ, IL-4 and TGF-α in multiple sclerosis in relation to HLA-Dw2 phenotype and stage of disease. *Mult Scler* **1**: 173–180
Söderström M, Ya-Ping J, Hillert J, Link H 1998 Optic neuritis: prognosis for multiple sclerosis from MRI, CSF and HLA findings. *Neurology* **50**: 708–714
Sohal RS, Weindruch R 1996 Oxidative stress, caloric restriction, and aging. *Science* **273**: 59–63
Soilu-Hanninen M, Salmi A, Salonen R 1995 Interferon-beta downregulates expression of VLA-4 antigen and antagonizes interferon-gamma-induced expression of HLA-DQ on human peripheral blood monocytes. *J Neuroimmunol* **60**: 99–106
Sokic DV, Stojsavljevic N, Drulovic J *et al* 2001 Seizures in multiple sclerosis. *Epilepsia* **42**: 72–79
Solansky M, Maeda Y, Ming X *et al* 2001 Proliferating oligodendrocytes are present in both active and chronic inactive multiple sclerosis plaques. *J Neurosci Res* **15**: 65: 308–317
Solaro C, Tanganelli P 2004 Tiagabine for treating painful tonic spasms in multiple sclerosis: a pilot study. *J Neurol Neurosurg Psychiatry* **75**: 341
Solaro C, Lunardi GL, Capello E *et al* 1998 An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* **51**: 609–611
Solaro C, Uccelli MM, Guglieri P *et al* 2000 Gabapentin is effective in treating nocturnal painful spasms in multiple sclerosis. *Mult Scler* **6**: 192–193
Solaro C, Brichetto G, Amato MP *et al* 2004 The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. *Neurology* **63**: 919–921
Solaro C, Allemani C, Messmer-Ucelli M *et al* 2005 The prevalence of multiple sclerosis in the north-west Italian province of Genoa. *J Neurol* **252**: 436–440
Soldan SS, Berti R, Salem N *et al* 1997 Association of human herpes virus 6 (HHV-6) with multiple sclerosis: increased IgM response to HHV-6 early antigen and detection of serum HHV-6 DNA. *Nature Med* **3**: 1394–1397
Soldan SS, Leist TP, Juhng KN *et al* 2000 Increased lymphoproliferative response to human herpesvirus type 6A variant in multiple sclerosis patients. *Ann Neurol* **47**: 306–313
Soliven B, Albert J 1992 Tumor necrosis factor modulates Ca^{2+} currents in cultured sympathetic neurons. *J Neurosci* **123**: 2665–2671
Sommer C, Schmidt C, George A 1998 Hyperalgesia in experimental neuropathy is dependent on the TNF receptor 1. *Exp Neurol* **151**: 138–142
Sommerlund M, Pallesen G, Moller-Larsen A *et al* 1993 Retrovirus-like particles in an Epstein–Barr virus producing cell line derived from a patient with chronic progressive myelopathy. *Acta Neurol Scand* **87**: 71–76
Song H, Stevens CF, Gage FH 2002 Astroglia induce neurogenesis from adult neural stem cells. *Nature* **417**: 39–44
Song M-R, Ghosh A 2004 FGF2-induced chromatin remodeling regulates CNTF-mediated gene expression and astrocyte differentiation. *Nat Neurosci* **7**: 229–235
Song P, Lie-Cheng W, Wang GD *et al* 2002 Interleukin-2 regulates membrane potentials and calcium channels via mu opioid receptors in rat dorsal root ganglion neurons. *Neuropharmacology* **43**: 1324–1329
Sonnenberg B 1991 *Lost Property: Memoirs and Confessions of a Bad Boy*. London: Faber & Faber
Soos JM, Ashley TA, Morrow J *et al* 1999 Differential expression of B7 co-stimulatory molecules by astrocytes correlates with T cell activation and cytokine production. *Int Immunol* **11**: 1169–1179
Sorensen PS, Wanscher B, Szpirt W *et al* 1996 Plasma exchange combined with azathioprine in multiple sclerosis using serial gadolinium-enhanced MRI to monitor disease activity: a randomized single-masked cross-over pilot study. *Neurology* **46**: 1620–1625
Sorensen PS, Wanscher B, Jensen C *et al* 1998 Intravenous immunoglobulin G reduces MRI activity in relapsing multiple sclerosis. *Neurology* **50**: 1273–1281
Sorenson PS, Ross C, Clemmesen K *et al* 2003 Clinical importance of neutralising antibodies against interferon beta in patients with relapsing–remitting multiple sclerosis. *Lancet* **362**: 1184–1191
Sorensen PS, Haas J, Sellebjerg F *et al* 2004 IV immunoglobulins as add-on treatment to methylprednisolone for acute relapses in MS. *Neurology* **63**: 2028–2033
Sorensen PS, Koch-Henriksen N, Ross C *et al* 2005 Appearance and disappearance of neutralizing antibodies during interferon-beta therapy. *Neurology* **65**: 33–39
Sorensen TL, Tani M, Jensen J *et al* 1999 Expression of specific chemokines and chemokine receptors in the central nervous

system of multiple sclerosis patients. *J Clin Invest* **103**: 807–815
Sorensen TL, Roed H, Sellebjerg F 2002a Chemokine receptor expression on B cells and effect of interferon-beta in multiple sclerosis. *J Neuroimmunol* **122**: 125–131
Sorensen TL, Trebst C, Kivisäkk P *et al* 2002b Multiple sclerosis: a study of CXCL10 and CXCR3 co-localization in the inflamed central nervous system. *J Neuroimmunol* **127**: 59–68
Sorkin LS, Doom CM 2000 Epineurial application of TNF elicits an acute mechanical hyperalgesia in the awake rat. *J Periph Nerv Syst* **5**: 96–100
Sorkin LS, Xiao WH, Wagner R, Myers RR 1997 Tumour necrosis factor-alpha induces ectopic activity in nociceptive primary afferent fibres. *Neuroscience* **81**: 255–262
Sormani MP, Molyneux PD, Gasperini C *et al* 1999 Statistical power of MRI monitored trials in multiple sclerosis: new data and comparison with previous results. *J Neurol Neurosurg Psychiatry* **66**: 465–469
Sornas R, Ostlund H 1972 The cytology of the cerebrospinal fluid. *Acta Neurol Scand* **48**: 81–89
Sosa Enriquez M, Leon Betancor P, Rosas C, Navarro MC 1983 La esclerosis multiple en la provincia de Las Palmas. *Arch Neurobiol* **46**: 161–166
Sospedra M, Martin R 2005 Immunology of multiple sclerosis. *Annu Rev Immunol* **23**: 683–747
Sotgiu S, Serra C, Marrosu MG *et al* 1999 Cytokine production in patients carrying multiple sclerosis-linked HLA-DR alleles. *J Neurol* **246**: 1194–1196
Sotgiu S, Piana A, Pugliatti M *et al* 2001a *Chlamydia pneumoniae* in the cerebrospinal fluid of patients with multiple sclerosis and neurological controls. *Mult Scler* **7**: 371–374
Sotgiu S, Pugliatti M, Solinas G *et al* 2001b Imunogenetic heterogeneity of multiple sclerosis in Sardinia. *Neurol Sci* **22**: 167–170
Sotgiu S, Pugliatti M, Rosati G, Sechi GP 2001c Which syringomyelia is truly associated with multiple sclerosis? *J Neurol Sci* **190**: 99–100
Sotgiu S, Serra C, Mameli G *et al* 2002 Multiple sclerosis-associated retrovirus and MS prognosis: an observational study. *Neurology* **59**: 1071–1073
Souberbielle BE, Martin-Mondiere C, O'Brien ME *et al* 1990 A case–control epidemiological study of MS in the Paris area with particular reference to past disease history and profession. *Acta Neurol Scand* **82**: 303–310
Soula C, Danesin C, Kan P *et al* 2001 Distinct sites of origin of oligodendrocytes and somatic motoneurons in the chick spinal cord: oligodendrocytes arise from Nkx2 2-expressing progenitors by a Shh-dependent mechanism. *Development* **128**: 1369–1379
Southwood C, He C, Garbern J *et al* 2004 CNS myelin paranodes require Nkx6–2 homeoprotein transcriptional activity for normal structure. *J Neurosci* **24**: 11215–11225
Sozzi G, Marotta P, Piatti L *et al* 1987 Paroxysmal sensory-motor attacks due to a spinal cord lesion identified by MRI. *J Neurol Neurosurg Psychiatry* **50**: 490–492
Spalding F 2001 *Gwen Raverat. Friends, family and affections*. London: Harvill Press
Spassky N, de Castro F, Le Bras BI *et al* 2002 Directional guidance of oligodendroglial migration by class 3 semaphorins and netrin-1. *J Neurosci* **22**: 5992–6004
Spatt J, Goldenberg G, Mamoli B 1995 Epilepsia partialis continua in multiple sclerosis. *Lancet* **345**: 658–659
Spector RH, Glaser JS, Schatz NJ 1980 Demyelinative chiasmal lesions. *Arch Neurol* **37**: 757–762
Spiegel J, Hansen C, Baumgartner U *et al* 2003 Sensitivity of laser-evoked potentials versus somatosensory evoked potentials in patients with multiple sclerosis. *Clin Neurophysiol* **114**: 992–1002
Spielman RS, McGinnis RE, Ewens WJ 1993 Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDMM). *Am J Hum Genet* **52**: 506–516
Spielmeyer W 1922 *Histopathologie des Nervensystems*. Berlin: Springer
Spies T, Bresnahan M, Bahram S *et al* 1990 A gene in the human histocompatibility complex class II region controlling the class I antigen presentation pathway. *Nature* **348**: 744–747
Spillane JD 1981 *The Doctrine of the Nerves: Chapters in the History of Neurology*. Oxford: Oxford University Press
Spillane JD, Wells CEC 1964 The neurology of Jennerian vaccination. *Brain* **87**: 1–44
Spissu A, Cannas A, Ferrigno P *et al* 1999 Anatomic correlates of painful tonic spasms in multiple sclerosis. *Mov Disord* **14**: 331–335
Spitsin SV, Hooper DC, Mikheeva T, Koprowski H 2001 Uric acid levels in patients with multiple sclerosis: analysis in mono- and dizygotic twins. *Mult Scler* **7**: 165–166
Spitsin SV, Scott GS, Kean RB *et al* 2000 Protection of myelin basic protein immunized mice from free-radical mediated inflammatory cell invasion of the central nervous system by the natural peroxynitrite scavenger uric acid. *Neurosci Lett* **292**: 137–141
Spitzer NC 1999 New dimensions of neuronal plasticity. *Nat Neurosci* **2**: 489–491
Spoor TC, Rockwell DL 1988 Treatment of optic neuritis with intravenous megadose corticosteroids. *Ophthalmology* **95**: 131–134
Sprawson CA 1927 Disseminated sclerosis in India. *Trans 7th Congress Far East Assoc Trop Med* **1**: 5 (abstract)
Sprent J, Surh CD 2002 T cell memory. *Annu Rev Immunol* **20**: 551–579
Springer TA 1994 Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. *Cell* **76**: 301–314
Sprinkle T, Wells M, Garver F, Smith D 1980 Studies on Wolfgram high molecular weight CNS proteins: relationship to 2'-3'-cyclic nucleotide 3'-phosphohydrolase. *J Neurochem* **35**: 1200–1208
Spuler S, Yousry T, Scheller A *et al* 1996 Multiple sclerosis: prospective analysis of TNF-alpha and 55 kDa TNF receptor in CSF and serum in correlation with clinical and MRI activity. *J Neuroimmunol* **66**: 57–64
Spurkland A, Ronningen KS, Vandvik B *et al* 1991a HLA-DQA1 and HLA-DQB1 genes may jointly determine susceptibility to develop multiple sclerosis. *Hum Immunol* **30**: 69–75
Spurkland A, Tabira T, Ronningen KS *et al* 1991b HLA-DRB1, -DQA1, -DQB1, -DPA1, -DPA1 and -DPB1 genes in Japanese multiple sclerosis patients. *Tissue Antigens* **37**: 171–173
Spurkland A, Knutsen I, Undlien DE, Vardtal F 1994 No association of multiple sclerosis to alleles at the TAP2 locus. *Hum Immunol* **39**: 299–301
Srinivasan R, Sailasuta N, Hurd R *et al* 2005 Evidence of elevated glutamate in multiple sclerosis using magnetic resonance spectroscopy at 3T. *Brain* **128**: 1016–1025
Sriram S, Stratton CWQ, Yao S-Y *et al* 1999 *Chlamydia pneumoniae* infection of the central nervous system in multiple sclerosis. *Ann Neurol* **46**: 6–14
Sriram U, Barcellos LF, Villoslada P *et al* 2003 Pharmacogenomic analysis of interferon receptor polymorphisms in multiple sclerosis. *Genes Immun* **4**: 147–152
Stadelmann C, Kerschensteiner M, Misgeld T *et al* 2002 BDNF and gp145trkB in multiple sclerosis brain lesions: neuroprotective interactions between immune cells and neuronal cells? *Brain* **125**: 75–85
Stadelmann C, Ludwin S, Tabira T *et al* 2005 Tissue preconditioning may explain concentric lesions in Baló's type of multiple sclerosis. *Brain* **128**: 979–987
Staffen W, Mair A, Zauner H *et al* 2002 Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. *Brain* **125**: 1275–1282
Stahl JS, Rottach KG, Averbuch-Heller L *et al* 1996 A pilot study of gabapentin as treatment for acquired nystagmus. *Neuroophthalmology* **16**: 107–113
Stahl SM, Johnson KP, Malamud N 1980 The clinical and pathological spectrum of brain-stem vascular malformations: long term course simulates multiple sclerosis. *Arch Neurol* **37**: 25–29
Stalder AK, Carson MJ, Pagenstecher A *et al* 1998 Late-onset chronic inflammatory encephalopathy in immune-competent and severe combined immune-deficient (SCID) mice with astrocyte-targeted expression of tumor necrosis factor. *Am J Pathol* **153**: 767–783
Stamler JS, Simon DI, Osborne JA *et al* 1992 S-nitrosylation of proteins with nitric oxide:

synthesis and characterization of biologically active compounds. *Proc Natl Acad Sci USA* **89**: 444–448

Stammers M, Rowen L, Rhodes D *et al* 2000 *BTL-II*: a polymorphic locus with homology to the butyrophilin gene family, located at the border of the major histocompatibility complex class II and class III regions in human and mouse. *Immunogenetics* **51**: 373–382

Stangel M, Compston A 2001 Polyclonal immunoglobulins (IVIg) modulate nitric oxide production and microglial functions in vitro via Fc receptors. *J Neuroimmunol* **112**: 63–71

Stangel M, Hartung HP 2002 [Intravenous immunoglobulins in multiple sclerosis: studies and mechanisms of action – an update]. *Nervenarzt* **73**: 119–124

Stangel M, Compston A, Scolding NJ 1999 Polyclonal immunoglobulins for intravenous use do not influence the behaviour of cultured oligodendrocytes. *J Neuroimmunol* **96**: 228–233

Stangel M, Boegner F, Klatt CH *et al* 2000a Placebo controlled pilot trial to study the remyelinating potential of intravenous immunoglobulins in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **68**: 89–92

Stangel M, Joly E, Scolding NJ, Compston DAS 2000b Normal polyclonal immunoglobulins ('ivIG') inhibit microglial phagocytosis *in vitro*. *J Neuroimmunol* **106**: 137–144

Stanislaus R, Singh AK, Singh I 2001 Lovastatin treatment decreases mononuclear cell infiltration into the CNS of Lewis rats with experimental allergic encephalomyelitis. *J Neurosci Res* **66**: 155–162

Stankoff B, Aigrot MS, Noel F *et al* 2002a Ciliary neurotrophic factor (CNTF) enhances myelin formation: a novel role for CNTF and CNTF-related molecules. *J Neurosci* **22**: 9221–9227

Stankoff B, Barron S, Allard J *et al* 2002b Oligodendroglial expression of Edg-2 receptor: developmental analysis and pharmacological responses to lysophosphatidic acid. *Mol Cell Neurosci* **20**: 415–28

Stankoff B, Waubant E, Confavreux C *et al* 2005 Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. *Neurology* **64**: 1139–1143

Stanley GP, Pender MP 1991 The pathophysiology of chronic relapsing experimental allergic encephalomyelitis in the Lewis rat. *Brain* **114**: 1827–1853

Staples D, Lincoln NB 1979 Intellectual impairment in multiple sclerosis and its relation to functional abilities. *Rheumatol Rehab* **18**: 153–160

Starck M, Albrecht H, Pollmann W *et al* 1997 Drug therapy for acquired pendular nystagmus in multiple sclerosis. *J Neurol* **244**: 9–16

Staugaitis SD, Roberts JK, Sacco RL, Miller JR 1998 Devic type multiple sclerosis in an 81 year old woman. *J Neurol Neurosurg Psychiatry* **64**: 417

Stazi MA, Cotichini R, Patriarca V *et al* 2002 The Italian twin project: from the personal identification number to a national twin registry. *Twin Res* **5**: 382–386

Stazio A, Kurland LT, Bell GL *et al* 1964 Multiple sclerosis in Winnipeg, Manitoba. Methodological consideration of epidemiologic survey: ten-year follow-up of a community-wide study and population re-survey. *J Chronic Disease* **17**: 415–438

Steck B Amsler F, Kappos L, Burgin D 2001 Gender-specific differences in the process of coping in families with a parent affected by a chronic somatic disease (e.g multiple sclerosis). *Psychopathology* **34**: 236–244

Steckley JL, Dyment DA, Sadovnick *et al* 2000 Genetic analysis of vitamin D related genes in Canadian multiple sclerosis patients. Canadian Collaborative Study Group. *Neurology* **54**: 729–732

Stefferl A, Brehm U, Storch M *et al* 1999 Myelin oligodendrocyte glycoprotein induces experimental autoimmune encephalomyelitis in the resistant Brown Norway rat: disease susceptibility is determined by MHC and MHC-linked effects on the B-cell response. *J Immunol* **163**: 40–49

Stefferl A, Schubart A, Storch M *et al* 2000 Butyrophilin, a milk protein, modulates the encephalitogenic T cell response to myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis. *J Immunol* **165**: 2859–2865

Stefoski D, Davis FA, Faut M, Schauf CL 1987 4-aminopyridine in patients with multiple sclerosis. *Ann Neurol* **21**: 71–81

Stefoski D, Davis FA, Fitzsimmons WE, Luskin SS, Rush J, Parkhurst GW 1991 4-aminopyridine in multiple sclerosis: prolonged administration. *Neurology* **41**: 1344–1348

Stein EC, Schiffer RB, Hall WJ, Young N 1987 Multiple sclerosis and the workplace: report of an industry-based cluster. *Neurology* **37**: 1672–1677

Stein R, Nordal HJ, Oftedal, Slettebo M 1987 The treatment of spasticity in multiple sclerosis: a double blind clinical trial of a new anti-spastic drug tizanidine compared with baclofen. *Acta Neurol Scand* 75: 190–194

Steindler DA, Pincus DW 2002 Stem cells and neuropoiesis in the adult human brain. *Lancet* **359**: 1047–1054

Steiner G 1931 Regionale Verteilung der Entmarkungsherde in ihrer Bedeutung für die Pathogenese der multiplen Sklerose. *Krankheitserreger und Gewebsbefund bei multipler Sklerose*. Berlin: Springer, pp. 108–120

Steiner I, Nisipianu P, Wirguin I 2001 Infection and the etiology and pathogenesis of multiple sclerosis. *Curr Neurol Neurosci Rep* **1**: 271–276

Steiniger B, Van der Meide PH 1988 Rat ependyma and microglia cells express class II MHC antigens after intravenous infusion of recombinant gamma interferon. *J Neuroimmunol* **19**: 111–118

Steinman L 2003 Optic neuritis, a new variant of experimental encephalomyelitis, a durable model for all seasons, now in its seventieth year. *J Exp Med* **197**: 1065–1071

Steinman L 2005 Blocking adhesion molecules as therapy for multiple sclerosis: natalizumab. *Nat Rev Drug Discov* **4**: 510–508

Steinman RM, Cohn ZA 1973 Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. *J Exp Med* **137**: 1142–1162

Stenager E, Knudson L, Jensen K 1991 Acute and chronic pain syndromes in multiple sclerosis. *Acta Neurol Scand* **84**: 197–200

Stenager E, Stenager EN, Jensen K 1996 Sexual function in multiple sclerosis: a 5-year follow-up study. *Ital J Neurol Sci* **17**: 67–69

Stenager E, Bronnum-Hansen H, Koch-Henriksen N 2003 The risk of multiple sclerosis in nurses: a population-based epidemiological study. *Mult Scler* **9**: 299–301

Stenager EN, Stenager E, Koch-Henriksen N *et al* 1992 Suicide and multiple sclerosis. *J Neurol Neurosurg Psychiatry* **55**: 542–545

Stendahl L, Link H, Moller E, Norrby E 1976 Relation between genetic markers and oligoclonal IgG in CSF in optic neuritis. *J Neurol Sci* **27**: 93–98

Stendahl-Brodin L, Link H 1983 Optic neuritis: oligoclonal bands increase the risk of multiple sclerosis. *Acta Neurol Scand* **67**: 301–304

Stephanova DI, Chobanova M 1997 Action potentials and ionic currents through paranodally demyelinated human motor nerve fibres: computer simulations. *Biol Cybernetics* **76**: 311–314

Sterman AB, Coyle PK, Panesci DJ, Grimson R 1985 Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. *Neurology* **35**: 1665–1668

Steultjens EM, Dekker J, Bouter LM *et al* 2003 Occupational therapy for multiple sclerosis. *Cochrane Database Syst Rev* **3:** CD003608

Stevens B, Porta S, Haak LL *et al* 2002 Adenosine: a neuron-glial transmitter promoting myelination in the CNS in response to action potentials. *Neuron* **36**: 855–868

Stevenson VL, Acheson JF, Ball J, Plant GT 1996 Optic neuritis following measles/rubella vaccination in two 13-year-old children. *Br J Ophthalmol* **80**: 1110–1111

Stevenson VL, Gawne-Cain ML, Barker GJ, Thompson AJ, Miller DH 1997 Imaging of the spinal cord and brain in multiple sclerosis: a comparison study between fast flair and fast spin echo. *J Neurol* **244**: 119–124

Stevenson VL, Miller DH, Rovaris M *et al* 1999 Primary and transitional progressive MS: a clinical and MRI cross-sectional study. *Neurology* **52** : 839–845

Stevenson VL, Miller DH, Leary SM *et al* 2000 One year follow up study of primary and

transitional progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* **68**: 713–718
Stewart GJ, Basten A, Bashir HV *et al* 1977 HLA-DW2, viral immunity and family studies in multiple sclerosis. *J Neurol Sci* **32**: 153–167
Stewart GJ, McLeod JG, Basten A, Bashir HE 1981 HLA family studies in multiple sclerosis: a common gene, dominantly expressed. *Hum Immunol* **3**: 13–29
Stewart GJ, Teutsch SM, Castle M, Heard RNS, Bennetts BH 1997 HLA-DR, -DQA1 and DQB1 associations in Australian multiple sclerosis patients. *Eur J Immunogenet* **24**: 81–92
Stewart VC, Giovannoni G, Land JM *et al* 1997 Pretreatment of astrocytes with interferon-alpha/beta impairs interferon-gamma induction of nitric oxide synthase. *J Neurochem* **68**: 2547–2551
Stewart VC, Land JM, Clark JB, Heales SJR 1998 Pretreatment of astrocytes with interferon-α/β prevents neuronal mitochondrial respiratory chain damage. *J Neurochem* **68**: 2547–2551
Stewart WA, Hall LD, Berry K 1986 Magnetic resonance imaging (MRI) in multiple sclerosis (MS): pathological correlation studies in eight cases. *Neurology* **36**: 320
Stidworthy MF, Genoud S, Li WW *et al* 2004 Notch1 and Jagged1 are expressed after CNS demyelination, but are not a major rate-determining factor during remyelination. *Brain* **127**: 1928–1941
Stinissen P, Vandevyver C, Medaer R *et al* 1995 Increased frequency of γδ T cells in cerebrospinal fluid and peripheral blood of patients with multiple sclerosis: reactivity, cytotoxicity, and T cell receptor V gene rearrangements. *J Immunol* **154**: 4883–4849
Stohl W, Gonatas NK 1978 Chronic permeability of the central nervous system to mononuclear cells in experimental allergic encephalomyelitis in the Lewis rat. *J Immunol* **120**: 844–850
Stolp-Smith KA 1998 Lifetime care needs of individuals with multiple sclerosis. *J Spinal Cord Med* **21**: 121–123
Stolp-Smith KA, Carter JL, Rohe DE, Knowland DP 1997 Management of impairment, disability, and handicap due to multiple sclerosis. *Mayo Clin Proc* **72**: 1184–1196
Stolt CC, Lommes P, Sock E *et al* 2003 The Sox9 transcription factor determines glial fate choice in the developing spinal cord. *Genes Dev* **17**: 1677–1689
Stone J, Sharpe M, Carson A *et al* 2002 Are functional motor and sensory symptoms really more frequent on the left? A systematic review. *J Neurol Neurosurg Psychiatry* **73**: 578–581
Stone J, Sharpe M, Rothwell PM, Warlow CP 2003 The 12 year prognosis of unilateral functional weakness and sensory disturbance. *J Neurol Neurosurg Psychiatry* **74**: 591–596
Stone LA, Frank JA, Albert PS *et al* 1995 The effect of interferon-β on blood brain barrier disruptions demonstrated by contrast-enhanced magnetic resonance imaging in relapsing–remitting multiple sclerosis. *Ann Neurol* **37**: 611–619
Stone LA, Frank JA, Albert PS *et al* 1997 Characterisation of MRI response to treatment with interferon beta-1b: contrast-enhancing MRI lesion frequency as a primary outcome measure. *Neurology* **49**: 862–869
Stone SH, Lerner EM 1965 Chronic disseminated allergic encephalomyelitis in guinea pigs. *Ann NY Acad Sci* **122**: 227–241
Storch MK, Piddlesden S, Haltia M *et al* 1998a Multiple sclerosis: *in situ* evidence for antibody and complement mediated demyelination. *Ann Neurol* **43**: 465–471
Storch MK, Stefferl A, Brehm U *et al* 1998b Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. *Brain Pathol* **8**: 681–694
Strachan JR, Pryor JP 1987 Diagnostic intracorporeal papaverine and erectile dysfunction. *Br J Urol* **59**: 264–266
Stransky E 1903 Über diskontinuierliche Zerfallsprozesse an der peripheren Nervenfaser. *J Psychol Neurol (Leipzig)* **1**: 169–199
Strasser-Fuchs S, Fazekas F, Flooh E *et al* 1997 Die Einstellung von Patienten mit multipler Sklerose zur Krankheitsaufklärung. *Nervenarzt* **68**: 963–966
Stratton K, Almario DA, McCormick MC (eds) 2002 *Immunization Satefy Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders*. Washington, DC: National Academies Press
Striano P, Striano S, Carreieri PB, Boccella P 2003 Epilepsia partialis continua as a first symptom of multiple sclerosis: electrophysiological study of one case. *Mult Scler* **9**: 199–203
Strijbos PJ, Leach MJ, Garthwaite J 1996 Vicious cycle involving Na+ channels, glutamate release, and NMDA receptors mediates delayed neurodegeneration through nitric oxide formation. *J Neurosci* **16**: 5004–5013
Strober W, Ehrhardt RO 1993 Chronic intestinal inflammation: an unexpected outcome in cytokine or T cell receptor mutant mice. *Cell* **75**: 203–205
Strumpell A 1896 Zür pathologie den multiplen Sklerose. *Neurolisches Zentralblatt* **15**: 961–964
Strumpell A 1931 *A Practice of Medicine* (ranslated from the 30th German edition by C.F. Marshall and C.M. Ottley). London: Baillière, Tindall & Cox, pp. 1833–1844
Sturkenboom MCJM, Abenhaim L, Wolfson C *et al* 1999 Vaccinations, demyelination and multiple sclerosis study (VDAMS): a population-based study in the UK. *Pharmacoepidemiol Drug Safety* **8(Suppl)**: S170–S171
Sturkenboom MC, Wolfson C, Roullet E *et al* 2000 Demyelination, multiple sclerosis, and hepatitis B vaccination: a population-based study in the UK. *Neurology* **54 (Suppl 3)**: A166
Stürzebecher S, Wandinger KP, Rosenwald A *et al* 2003 Expression profiling identifies responder and non-responder phenotypes to interferon-beta in multiple sclerosis. *Brain* **126**: 1419–1429
Stuve O, Dooley NP, Uhm JH *et al* 1996 Interferon β-1b decreases the migration of T lymphocytes *in vitro*: effects on matrix metalloproteinase-9. *Ann Neurol* **40**: 853–863
Stuve O, Chabot S, Jung SS *et al* VW 1997 Chemokine-enhanced migration of human peripheral blood mononuclear cells is antagonized by interferon beta-1b through an effect on matrix metalloproteinase-9. *J Neuroimmunol* **80**: 38–46
Stys P 2004 Axonal degeneration in multiple sclerosis: is it time for neuroprotective strategies? *Ann Neurol* **55**: 601–603
Stys PK, LoPachin RM 1997 Mechanisms of calcium and sodium fluxes in anoxic myelinated central nervous system axons. *Neuroscience* **82**: 21–32
Stys PK, Waxman SG, Ransom BR 1991 Na(+)-Ca2+ exchanger mediates Ca2+ influx during anoxia in mammalian central nervous system white matter. *Ann Neurol* **30**, 375–380
Stys PK, Sontheimer H, Ransom BR, Waxman SG 1993 Noninactivating, tetrodotoxin-sensitive Na+ conductance in rat optic nerve axons. *Proc Natl Acad Sci USA* **90**: 6976–6980
Su Y, Ganea D, Peng X, Jonakait M 2003 Galanin down-regulates microglial tumor necrosis factor-α production by a post-transcriptional mechanism. *J Neuroimmunol* **134**: 52–60
Suarez B, Hodge S 1979 A simple method to detect linkage for rare recessive diseases: an application to juvenile diabetes. *Clin Genet* **15**: 126–136
Subramaniam A, Harris A, Pignatelli E *et al* 2003 Metastasis to and from the central nervous system – the 'relatively protected site'. *Lancet Oncol* **3**: 498–507
Subramanian G, Adams MD, Venter JC, Broder S 2001 Implications of the human genome for understanding human biology and medicine. *J Am Med Assoc* **286**: 2296–2307
Suda H, Hosokawa T, Ohno R, Hamaguchi K, Tsukada Y 1984 2',3'-Cyclic nucleotide 3'-phosphodiesterase activity in the cerebrospinal fluid of patients with demyelinating diseases. *Neurochem Pathol* **2**: 85–102
Sudomoina MA, Boiko AN, Demina TL *et al* 1998 Association of multiple sclerosis in the Russian population with HLA-DRB1 gene alleles. *Mol Biol* **32**: 255–260
Sudweeks JD, Todd JA, Blankenhorn EP *et al* 1993 Locus controlling *Bordetella pertussis*-induced histamine sensitization (*Bphs*), and autoimmune disease susceptibility gene, maps to T-cell receptor β-chain gene on mouse chromosome 6. *Proc Natl Acad Sci USA* **90**: 3700–3704

Suen WE, Bergman CM, Hjelmström P, Ruddle NH 1997 A critical role for lymphotoxin in experimental allergic encephalomyelitis. *J Exp Med* **186**: 1233–1240

Sugano M, Hirayama K, Saito T *et al* 1992 Necrotic plaque formation in a case of frontal lobe multiple sclerosis. *Rinsho Shinkeigaku* **32**: 621–625

Sugawa M, Sakurai Y, Ishikawa-Ieda Y *et al* 2002 Effects of erythropoietin on glial cell development: oligodendrocyte maturation and astrocyte proliferation. *Neurosci Res* **44**: 391–403

Sullivan F, Hutchinson M, Bahandeka S, Moore RE 1987 Chronic hypothermia in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **50**: 813–815

Sullivan PG, Bruce-Keller AJ, Rabchevsky AG *et al* 1999 Exacerbation of damage and altered NF-kB activation in mice lacking tumor necrosis factor receptors after traumatic brain injury. *J Neurosci* **19**: 6248–6256

Sumelahti M-L, Tienari PJ, Wikstrom J *et al* 2000 Regional and temporal variation in the incidence of multiple sclerosis in Finland 1979–1993. *Neuroepidemiology* **19**: 67–75

Sumelahti M-L, Tienari PJ, Wikstrom J *et al* 2001 Increasing prevalence of multiple sclerosis in Finland. *Acta Neurol Scand* **103**: 153–158

Sumelahti M-L, Tienari PJ, Wikstrom J *et al* 2002 Survival of multiple sclerosis in Finland between 1964–1993. *Mult Scler* **8**: 350–355

Summerfield R, Tubridy N, Sirker A *et al* 2002 Pulmonary oedema with multiple sclerosis. *J R Soc Med* **95**: 401–402

Sumner AJ, Saida K, Saida T *et al* 1982 Acute conduction block associated with experimental antiserum-mediated demyelination of peripheral nerve. *Ann Neurol* **11**: 469–477

Sun D, Wekerle H 1986 Ia-restricted encephalitogenic T-lymphocytes mediating EAE lyse autoantigen presenting astrocytes. *Nature* **320**: 70–72

Sun D, Qin Y, Chluba J, Epplen JT, Wekerle H 1988 Suppression of experimentally induced autoimmune encephalomyelitis by cytolytic T-T- cell interactions. *Nature* **332**: 843–845

Sun D, Gold DP, Smith L *et al* 1992 Characterization of rat encephalitogenic T cells bearing non-Vβ8 T cell receptors. *Eur J Immunol* **22**: 591–594

Sun D, Hu X-Z, Coleclough C 1995 The clonal composition of myelin basic protein-reactive encephalitogenic T cell populations is influenced both by the structure of relevant antigens and the nature of antigen-presenting cells. *Eur J Immunol* **25**: 69–74

Sun D, Whitaker JN, Huang Z *et al* 2001 Myelin antigen specific CD8+ T cells are encephalitogenic and produce severe disease in C57Bl/6 mice. *J Immunol* **166**: 7579–7587

Sun J, Olsson T, Wang W-Z *et al* 1991a Autoreactive T and B cells responding to myelin proteolipid protein in multiple sclerosis and controls. *Eur J Immunol* **21**: 1461–1468

Sun J, Link H, Olsson H *et al* 1991b T and B cell responses to myelin-oligodendrocyte glycoprotein in multiple sclerosis. *J Immunol* **146**: 1490–1495

Sun T, Pringle NP, Hardy AP *et al* 1998 Pax6 influences the time and site of origin of glial precursors in the ventral neural tube. *Mol Cell Neurosci* **12**: 228–239

Sun Y, Goderie SK, Temple S 2005 Asymmetric distribution of EGFR recptor during mitosis generates diverse CNS progenitor cells. *Neuron* **45**: 873–886

Sundstrom P, Nystrom L, Forsgren L 2003 Incidence (1988–97) and prevalence (1997) of multiple sclerosis in Vasterbotten County in northern Sweden. *J Neurol Neurosurg Psychiatry* **74**: 29–32

Sundvall M, Jirholt J, Yang HT *et al* 1995 Identification of murine loci associated with susceptibility to chronic experimental autoimmune encephalomyelitis. *Nature Genet* **10**: 313–317

Sunku J, Kurland LT 1994 Multiple sclerosis and trauma (letter). *Neurology* **44**: 2416

Suppiah V, Alloza I, Heggarty S *et al* 2005 The CTLA4 +49 A/G*G-CT60*G haplotype is associated with susceptibility to multiple sclerosis in Flanders. *J Neuroimmunol* **164**: 148–153

Surridge D 1969 An investigation into some psychiatric aspects of multiple sclerosis. *Br J Psychiatry* **115**: 749–764

Susac JO, Murtagh FR, Egan RA *et al* 2003 MRI findings in Susac's syndrome. *Neurology* **61**: 1783–1787

Sussman CR, Vartanian T, Miller RH 2005 The ErbB4 neuregulin receptor mediates suppression of oligodendrocyte maturation. *J Neurosci* **25**: 5757–5762

Sussmuth SD, Reiber H, Tumani H 2001 Tau protein in cerebrospinal fluid (CSF): a blood-CSF barrier related evaluation in patients with various neurological diseases. *Neurosci Lett* **300**: 95–98

Sutherland JM 1956 Observations on the prevalence of multiple sclerosis in northern Scotland. *Brain* **79**: 635–654

Sutherland JM 1989 *A Far Off Sunlit Place*, Brisbane: Amphion Press

Sutherland JM, Tyrer JH, Eadie MJ *et al* 1966 The prevalence of multiple sclerosis in Queensland, Australia: a field survey. *Acta Neurol Scand* **42 (Suppl 19)**: 57–67

Sutkowski N, Conrad B, Thorley-Lawson DA, Huber BT 2001 Epstein–Barr virus transactivates the human endogenous retrovirus HERV-K18 that encodes a superantigen. *Immunity* **15**: 579–589

Suzuki K, Andrews JM, Waltz JM, Terry RD 1969 Ultrastructural studies of multiple sclerosis. *Lab Invest* **20**: 444–454

Svendsen KB, Jensen TS, Overvad K *et al* 2003 Pain in patients with multiple sclerosis: a population-based study. *Arch Neurol* **60**: 1089–1094

Svenningsson A, Runmarker B, Lycke J, Andersen O 1990 Incidence of MS during two fifteen-year periods in the Gothenburg region of Sweden. *Acta Neurol Scand* **82**: 161–168

Svenningsson A, Hansson GK, Andersen O *et al* 1993 Adhesion molecule expression on cerebrospinal fluid T lymphocytes: evidence for common recruitment mechanisms in multiple sclerosis, aseptic meningitis and normal controls. *Ann Neurol* **34**: 155–161

Svenningsson A, Petersson AS, Andersen O, Hansson GK 1999 Nitric oxide metabolites in CSF of patients with MS are related to clinical disease course. *Neurology* **53**: 1880–1882

Swanborg RH, Whittum-Hudson JA, Hudson AP 2003 Infectious agents and multiple sclerosis – are *Chlamydia pneumoniae* and human herpes virus 6 involved? *J Neuroimmunol* **136**: 1–8

Swank RL 1953 Treatment of multiple sclerosis with low fat diet. *Arch Neurol Psychiatry* **69**: 91–103

Swanton JK, Fernando K, Dalton CM *et al* 2005 Modification of MRI criteria for MS in patients with clinically isolated syndromes. *J Neurol Neurosurg Psychiatry* [epub ahead of print]

Sweeney VP, Sadovnick AD, Brandejs V 1986 Prevalence of multiple sclerosis in British Columbia. *Can J Neurol Sci* **13**: 47–51

Sweeney WJ 1955 Pregnancy and multiple sclerosis. *Am J Obstetr Gynecol* **66**: 124–130

Swinburn WR, Liversedge LA 1973 Long-term treatment of multiple sclerosis with azathioprine. *J Neurol Neurosurg Psychiatry* **36**: 124–126

Swingler RJ, Compston DAS 1986 The distribution of multiple sclerosis in the United Kingdom. *J Neurol Neurosurg Psychiatry* **49**: 1115–1124

Swingler RJ, Compston DAS 1988 The prevalence of multiple sclerosis in South East Wales. *J Neurol Neurosurg Psychiatry* **51**: 1520–1524

Swingler RJ, Compston DAS 1992 The clinical features of multiple sclerosis in south east Wales. *Q J Med* **83**: 325–337

Sykes B 1999 The molecular genetics of European ancestry. *Phil Trans R Soc Lond* **354**: 131–139

Symon L, Kuyama H, Kendall B 1984 Dural arteriovenous malformations of the spine: clinical features and surgical results in 55 cases. *J Neurosurg* **60**: 238–247

Tabi Z, McCombe PA, Pender MP 1994 Apoptotic elimination of Vβ8.2$^+$ cells from the central nervous system during recovery from experimental autoimmune encephalomyelitis induced by passive transfer of Vβ8.2$^+$ encephalitogenic T cells. *Eur J Immunol* **24**: 2609–2617

Tabira T, Itoyama Y, Kuroiwa Y *et al* 1983 Delayed type skin response to myelin basic protein in chronic relapsing experimental allergic encephalomyelitis. *J Neuroimmunol* **5**: 295–304

Tabira T, Itoyama Y, Kuroiwa Y 1984 The role of locally retained antigens in chronic relapsing

experimental allergic encephalomyelitis in guinea pigs. In: Alvord EC, Kies MW, Suckling AJ (eds) *Experimental Allergic Encephalomyelitis: A Useful Model for Multiple Sclerosis?* New York: Allan Liss, pp. 43–48

Tachibana N, Howard RS, Hirsch NO, Miller DH, Moseley IF, Fish D 1994 Sleep problems in multiple sclerosis. *Eur Neurol* **34**: 320–323

Tagawa A, Ono S, Inoue K *et al* 2001 A new familial adult-onset leucodystrophy manifesting as cerebellar ataxia and dementia. *J Neurol Sci* **183**: 47–55

Taguchi O, Nishizuka Y 1980 Autoimmune oophoritis in thymectomized mice: T cell requirement in adoptive cell transfer. *Clin Exp Immunol* **42**: 324–331

Taguchi O, Nishizuka Y 1981 Experimental autoimmune orchitis after neonatal thymectomy in the mouse. *Clin Exp Immunol* **46**: 425–434

Taguchi O, Nishizuka Y 1987 Self tolerance and localized autoimmunity: mouse models of autoimmune disease that suggest tissue-specific suppressor T cells are involved in self tolerance. *J Exp Med* **165**: 146–156

Tahmoush AJ, Amir MS, Connor WW *et al* 2002 CSF-ACE activity in probable CNS neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* **19**: 191–197

Tajouri L, Mellick A, Ashton K *et al* 2003 Quantitative and qualitative changes in gene expression patterns characterize the activity of plaques in multiple sclerosis. *Mol Brain Res* **119**: 170–183

Tajouri L, Ferreira L, Ovcaric M *et al* 2004 Investigation of a neuronal nitric oxide synthase gene (NOS1) polymorphism in a multiple sclerosis population. *J Neurol Sci* **218**: 25–28

Tajouri L, Mellick AS, Tourtellotte A *et al* 2005 An examination of MS candidate genes identified as differentially regulated in multiple sclerosis plaque tissue, using absolute and comparative real-time Q-PCR analysis. *Brain Res Brain Res Protoc* **15**: 79–91

Takacs M, Kalman B, Gyodi E *et al* 1990 Association between the lack of HLA-DQw6 and the low incidence of multiple sclerosis in Hungarian Gypsies. *Immunogenetics* **31**: 383–385

Takahashi JL, Giuliani F, Power C *et al* 2003 Interleukin-1β promotes oligodendrocyte death through glutamate excitotoxicity. *Ann Neurol* **53**: 588–595

Takahashi PY, Kiemele LJ, Jones JP 2004 Wound care for elderly patients: advances and clinical applications for practicing physicians. *Mayo Clin Proc* **79**: 260–267

Takano R, Hisahara S, Namikawa K *et al* 2000 Nerve growth factor protects oligodendrocytes from tumor necrosis factor-alpha-induced injury through Akt-mediated signaling mechanisms. *J Biol Chem* **275**: 16360–16365

Takata T, Hirakawa M, Sakurai M, Kanazawa I 1999 Fulminant form of acute disseminated encephalomyelitis: successful treatment with hypothermia. *J Neurol Sci* **165**: 94–97

Takebayashi H, Yoshida S, Sugimori M *et al* 2000 Dynamic expression of basic helix-loop-helix Olig family members: implication of Olig2 in neuron and oligodendrocyte differentiation and identification of a new member, Olig3. *Mech Dev* **99**: 143–148

Takebayashi H, Nabeshima Y, Yoshida S *et al* 2002 The basic helix-loop-helix factor olig2 is essential for the development of motoneuron and oligodendrocyte lineages. *Curr Biol* **12**: 1157–1163

Talley CL 2005 The emergence of multiple sclerosis 1870–1950: a puzzle of historical epidemiology. *Perspect Biol Med* **48**: 383–395

Tan C-T 1988 Multiple sclerosis in Malaysia. *Arch Neurol* **45**: 624–627

Tan EM, Cohen AS, Fries JF *et al* 1982 The 1982 revised criteria for the diagnosis of systemic lupus erythematosus. *Arthritis Rheum* **25**: 1271–1277

Tan H, Kilicaslan B, Onbas O, Buyukavci M 2004 Acute disseminated encephalomyelitis following hepatitis A virus infection. *Pediatr Neurol* **30**: 207–209

Tan IL, Lycklama a Nijeholt GJ, Polman CH *et al* 2000 Linomide in the treatment of multiple sclerosis: MRI results from prematurely terminated phase-III trials. *Mult Scler* **6**: 99–104

Tan J, Town T, Paris D *et al* 1999 Activation of microglial cells by the CD40 pathway: relevance to multiple sclerosis. *J Neuroimmunol* **97**: 77–85

Tancredi V, D'Arcangelo G, Grassi F *et al* 1992 Tumor necrosis factor alters synaptic transmission in rat hippocampal slices. *Neurosci Lett* **146**: 176–178

Tanne D, D'Ohlaberriague L, Schultz L *et al* 1999 Anticardiolipin antibodies and their associations with cerebrovascular risk factors. *Neurology* **52**: 1368–1373

Tanuma N, Shin T, Matsumoto Y 2000 Characterization of acute versus chronic relapsing autoimmune encephalomyelitis in DA rats. *J Neuroimmunol* **108**: 171–180

Tao-Cheng JH, Brightman MW 1988 Development of membrane interactions between brain endothelial cells and astrocytes *in vitro*. *Int J Dev Neurosci* **6**: 5–37

Taphoorn MJ, van Someron E, Snoek FJ *et al* 1993 Fatigue, sleep disturbances and circadian rhythm in multiple sclerosis. *J Neurol* **240**: 446–448

Targ EF, Kocsis JD 1985 4-Aminopyridine leads to restoration of conduction in demyelinated rat sciatic nerve. *Brain Res* **328**: 358–361

Targ EF, Kocsis JD 1986 Action potential characteristics of demyelinated rat sciatic nerve following application of 4-aminopyridine. *Brain Res* **363**: 1–9

Targett MP, Sussman J, Scolding NJ *et al* 1996 Failure to remyelinate rat axons following transplantation of glial cells obtained from the adult human brain. *Neuropathol Appl Neurobiol* **22**: 199–206

Targoni OS, Lehmann PV 1998 Endogenous myelin basic protein inactivates the high avidity T cell repertoire. *J Exp Med* **187**: 2055–2063

Tartaglia MC, Narayanan S, Francis SJ *et al* 2004 The relationship between diffuse axonal damage and fatigue in multiple sclerosis. *Arch Neurol* **61**: 201–207

Tas MW, Barkhof F, Van den Walderveen MAA *et al* 1995 The effect of gadolinium on the sensitivity and specificity of MR imaging in the initial diagnosis of multiple sclerosis. *Am J Neuroradiol* **16**: 259–264

Tasaki I 1953 *Nervous Transmission*. Springfield, IL: C.C. Thomas

Tassinari T, Parodi S, Badino R, Vercelli M 2001 Mortalilty trend for multiple sclerosis in Italy (1974–1993). *Eur J Epidemiol* **17**: 105–110

Taub RG, Rucker CW 1954 The relationship of retrobulbar neuritis to multiple sclerosis. *Am J Ophthalmol* **32**: 488–497

Taupin V, Renno T, Bourbonniere L *et al* 1997 Increased severity of experimental autoimmune encephalomyelitis, chronic macrophage/microglia reactivity and demyelination in transgenic mice producing tumor necrosis factor-alpha in the central nervous system. *Eur J Immunol* **27**: 905–913

Tavolato B 1975 Immunoglobulin G distribution in multiple sclerosis brain: an immunofluorescence study. *J Neurol Sci* **24**: 1–11

Tazi-Ahnini R, Henry J, Offer C *et al* 1997 Cloning, localization, and structure of new members of the butyrophilin gene family in the juxta-telomeric region of the major histocompatibility complex. *Immunogenetics* **47**: 55–63

Teesalu T, Hinkkanen AE, Vaheri A 2001 Coordinated induction of extracellular proteolysis systems during experimental autoimmune encephalomyelitis in mice. *Am J Pathol* **159**: 2227–2237

Teitelbaum D, Webb C, Meshorer A *et al* 1973 Suppression by several synthetic polypeptides of experimental allergic encephalomyelitis induced in guinea pigs and rabbits with bovine and human basic encephalitogen. *Eur J Immunol* **3**: 273–279

Teitelbaum D, Aharoni R, Sela M, Arnon R 1991 Cross-reactions and specificities of monoclonal antibodies against myelin basic protein and against the synthetic copolymer 1. *Proc Natl Acad Sci USA* **88**: 9528–9532

Teitelbaum D, Fridkis-Hareli M, Arnon R, Sela M 1996 Copolymer 1 inhibits chronic relapsing experimental allergic encephalomyelitis induced by proteolipid protein (PLP) peptides in mice and interferes with PLP-specific T cell responses. *J Neuroimmunol* **64**: 209–217

Teitelbaum D, Brenner T, Abramsky O *et al* 2003 Antibodies to glatiramer acetate do not interfere with its biological functions and therapeutic efficacy. *Mult Scler* **9**: 592–599

Tejada-Simon MV, Zang YCQ, Hong J *et al* 2003 Cross-reactivity with myelin basic protein and human herpes virus-6 in multiple sclerosis. *Ann Neurol* **53**: 189–197

Tekki-Kessaris N, Woodruff R, Hall AC *et al* 2001 Hedgehog-dependent oligodendrocyte lineage specification in the telencephalon. *Development* **128**: 2545–2554

Telischi FF, Grobman LR, Sheremata WA *et al* 1991 Hemifacial spasm: occurrence in multiple sclerosis. *Arch Otolaryngol Head Neck Surg* **117**: 554–556

Templeton AR 2002 Out of Africa again and again. *Nature* **316**: 45–51

Tenembaum S, Chamoles N, Fejerman N 2002 Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. *Neurology* **59**: 1224–1231

Tenser RB, Hay KA, Aberg JA 1993 Immunoglobulin G immunosuppression of multiple sclerosis. *Arch Neurol* **50**: 417–420

Ter Braak JGW, van Herwaarden A 1933 Ophthalmo-encephalo-myelitis mit ungewönlichen Augenerscheinungen. *Klin Monatsbl Augenheilkd* **91**: 316–343

Ter Meulen V, Koprowski H, Iwasaki Y *et al* 1972 Fusion of cultured multiple sclerosis brain cells with indicator cells: presence of nucleocapsids and virions and isolation of parainfluenza-type virus. *Lancet* **ii**: 1–5

Terasaki PI, Park MS, Opelz G, Ting A 1976 Multiple sclerosis and high frequency of a B lymphocyte alloantigen. *Science* **193**: 1245–1247

Terwilliger JD, Zollner S, Laan M, Paabo S 1998 Mapping genes through the use of linkage disequilibrium generated by genetic drift: 'drift mapping' in small populations with no demographic expansion. *Hum Hered* **48**: 138–154

Tesar JT, McMillan V, Molina R, Armstrong J 1992 Optic neuropathy and central nervous system disease associated with primary Sjögren's syndrome. *Am J Med* **92**: 686–692

Teunissen CE, Dijkstra C, Polman C 2005 Biological markers in CSF and blood for axonal degeneration in multiple sclerosis. *Lancet Neurol* **4**: 32–41

Teutsch SM, Bennetts BH, Buhler MM *et al* 1999 The DRB1 Val86/Val86 genotype associates with multiple sclerosis in Australian patients. *Hum Immunol* **60**: 715–722

Teutsch SM, Booth DR, Bennetts BH *et al* 2003 Identification of 11 novel and common single nucleotide polymorphisms in the interleukin-7 receptor-alpha gene and their associations with multiple sclerosis. *Eur J Hum Genet* **11**: 509–515

Teutsch SM, Booth DR, Bennetts BH *et al* 2004 Association of common T cell activation gene polymorphisms with multiple sclerosis in Australian patients. *J Neuroimmunol* **148**: 218–230

Tharakan J, Ranganath PR, Jacob PC 2005 Multiple sclerosis in Oman. *Neurol J SE Asia* (in press)

Theien BE, Vanderlugt CL, Eagar TN *et al* 2001 Discordant effects of anti-VLA-4 treatment before and after onset of relapsing experimental autoimmune encephalomyelitis. *J Clin Invest* **107**: 995–1006

Thery C, Zitvogel L, Amigorena S 2002 Exosomes: composition, biogenesis and function. *Nat Rev Immunol* **2**: 569–579

Thiery E, de Reuck J 1974 Monoballism in multiple sclerosis. *Acta Neurol Belg* **74**: 241–249

Thomaides TN, Zoukos Y, Chaudhuri KR, Mathias CJ 1993 Physiological assessment of aspects of autonomic function in patients with secondary progressive multiple sclerosis. *J Neurol* **240**: 139–143

Thomas FJ, Wiles CM 1999 Dysphagia and nutritional status in multiple sclerosis. *J Neurol* **246**: 677–682

Thomas FJ, Hughes TA, Anstey A 2001 Azathioprine treatment in multiple sclerosis: pretreatment assessment of metaboliser status. *J Neurol Neurosurg Psychiatry* **70**: 815

Thomas PK, Walker RWH, Rudge PR *et al* 1987 Chronic demyelinating peripheral neuropathy associated with multifocal central nervous system demyelination. *Brain* **110**: 53–76

Thomke F, Lensch E, Ringel K, Hopf HC 1997 Isolated cranial nerve palsies in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **63**: 682–685

Thompson AJ 1998 Multiple sclerosis: rehabilitation measures. *Semin Neurol* **18**: 397–403

Thompson AJ 2002a Developing clinical outcome measures in multiple sclerosis: an evolving process. *Mult Scler* **8**: 357–358

Thompson AJ 2002b Progress in neurorehabilitation in multiple sclerosis. *Curr Opin Neurol* **15**: 267–270

Thompson AJ, Brazil J, Feighery C *et al* 1985 CSF myelin basic protein in multiple sclerosis. *Acta Neurol Scand* **72**: 577–583

Thompson AJ, Hutchinson M, Brazil J *et al* 1986 A clinical and laboratory study of benign multiple sclerosis. *Q J Med* **58**: 69–80

Thompson AJ, Kennard C, Swash M *et al* 1989 Relative efficacy of intravenous methylprednisolone and ACTH in the treatment of acute relapse in MS. *Neurology* **39**: 969–971

Thompson AJ, Smith I, Brenton D *et al* 1990a Neurological deterioration in young adults with phenylketonuria. *Lancet* **336**: 602–605

Thompson AJ, Kermode AG, Macmanus DG *et al* 1990b Patterns of disease activity in multiple sclerosis: clinical and magnetic resonance imaging study. *Br Med J* **300**: 631–634

Thompson AJ, Kermode AG, Wicks D *et al* 1991 Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Ann Neurol* **29**: 53–62

Thompson AJ, Miller D, Youl B *et al* 1992 Serial gadolinium-enhanced MRI in relapsing/remitting multiple sclerosis of varying disease duration. *Neurology* **42**: 60–63

Thompson AJ, Kermode AG, Moseley IF *et al* 1993a Seizures due to multiple sclerosis: seven patients with MRI correlation. *J Neurol Neurosurg Psychiatry* **56**: 1317–1320

Thompson AJ, Tillotson S, Smith I *et al* 1993b Brain MRI changes in phenylketonuria. *Brain* **116**: 811–821

Thompson AJ, Polman CH, Miller DH *et al* 1997 Primary progressive multiple sclerosis (review). *Brain* **120**: 1085–1096

Thompson AJ, Montalban X, Barkhof F *et al* 2000 Diagnostic criteria for primary progressive MS: a position paper. *Ann Neurol* **47**: 831–835

Thompson DS, Nelson LM, Burns A *et al* 1986 The effects of pregnancy in multiple sclerosis: a retrospective study. *Neurology* **36**: 1097–1099

Thompson EJ 1995 Cerebrospinal fluid. *J Neurol Neurosurg Psychiatry* **59**: 349–357

Thompson PD, Day BL, Rothwell JC *et al* 1987 The interpretation of electromyographic responses to electrical stimulation of the motor cortex in diseases of the upper motor neurone. *J Neurol Sci* **80**: 91–110

Thompson RJ, Mason CR, Douglas AJ *et al* 1996 Analysis of polymorphisms of the 2',3'-cyclic nucleotide-3'-phosphodiesterase gene in patients with multiple sclerosis. *Mult Scler* **2**: 215–221

Thomson CE, Vouyiouklis DA, Barrie JA *et al* 2005 Plp gene regulation in the developing murine optic nerve: correlation with oligodendroglial process alignment along the axons. *Dev Neurosci* **27**: 27–36

Thomson JA, Itskovitz-Eldor J, Shapiro SS *et al* 1998 Embryonic stem cell lines derived from human blastocysts. *Science* **282**: 1145–1147

Thorpe JW, Kidd D, Kendall BE 1993 Spinal cord MRI using multi-array coils and fast spin echo. I: Technical aspects and findings in healthy adults. *Neurology* **43**: 2625–2631

Thorpe JW, Mumford CJ, Compston DAS *et al* 1994a The British Isles survey of multiple sclerosis in twins: MRI findings. *J Neurol Neurosurg Psychiatry* **57**: 491–496

Thorpe JW, Moseley IF, Hawkes CH *et al* 1994b Brain and spinal cord magnetic resonance imaging in motor neurone disease. *J Neurol Neurosurg Psychiatry* **57**: 1298

Thorpe JW, Barker GJ, Jones SJ *et al* 1995 Magnetisation transfer ratios and transverse magnetisation decay curves in optic neuritis: correlation with clinical findings and electrophysiology. *J Neurol Neurosurg Psychiatry* **59**: 487–492

Thorpe JW, Kidd D, Moseley IF *et al* 1996a Serial gadolinium-enhanced MRI of the brain and spinal cord in early relapsing–remitting multiple sclerosis. *Neurology* **46**: 373–378

Thorpe JW, Kidd D, Moseley IF *et al* 1996b Spinal MRI in patients with suspected multiple sclerosis and negative brain MRI. *Brain* **119**: 709–714

Thorpe JW, Moseley IF, Hawkes CH *et al* 1996c Brain and spinal cord MRI in motor neuron disease. *J Neurol Neurosurg Psychiatry* **61**: 314–317

Thums K 1951 Einelige Zwillinge mit koncordanter multiplen Sklerose. *Wiener Z Nervenheilk* **4**: 173–203

Thygesen P 1949 Prognosis in initial stage of disseminated primary demyelinating disease of central nervous system. *Arch Neurol Psychiatry* **61**: 339–351

Thygesen P 1955 Disseminated sclerosis: influence of age on the different modes of progression. *Acta Psychiatr Neurol Scand* **30**: 365–374

Tiberio M, Chard DT, Altmann DR *et al* 2005 Gray and white matter volume change in early RRMS: a 2 year longitudinal study. *Neurology* **64**: 1001–1007

Tienari PJ, Salonen O, Wikstrom J *et al* 1992a Familial multiple sclerosis: MRI findings in clinically affected and unaffected siblings. *J Neurol Neurosurg Psychiatry* **55**: 883–886

Tienari PJ, Wikstrom J, Sajantila A *et al* 1992b Genetic susceptibility to multiple sclerosis linked to myelin basic protein gene. *Lancet* **340**: 987–991

Tienari PJ, Wikstrom J, Koskimies S *et al* 1993 Reappraisal of HLA in multiple sclerosis: close linkage in multiplex families. *Eur J Hum Genet* **1**: 257–268

Tienari PJ, Terwilliger JD, Ott J *et al* 1994 Two-locus linkage analysis in multiple sclerosis (MS). *Genomics* **19**: 320–325

Tienari PJ, Sumelahti ML, Rantamaki T, Wikstrom J 2004 Multiple sclerosis in western Finland: evidence for a founder effect. *Clin Neurol Neurosurg* **106**: 175–179

Tietjen I, Rihel JM, Cao YX *et al* 2003 Single-cell transcriptional analysis of neuronal progenitors. *Neuron* **38**: 161–175

Tillman AJB 1950 The effect of pregnancy on multiple sclerosis and its management. *Assoc Res Nerv Mental Dis* **28**: 548–582

Tilney F, Riley HA 1938 *The Form and Functions of the Central Nervous System*, 3rd edn. New York: Hoeber

Timme W and the Commission 1922 *Assoc Res Nerv Mental Dis* **2**: 47–48

Timsit S, Martinez S, Allinquant B *et al* 1995 Oligodendrocytes originate in a restricted zone of the embryonic ventral neural tube defined by DM-20 mRNA expression. *J Neurosci* **15**012–1024

Tincani A, Balestrieri G, Faden D, Di Mario C 1991 Systemic lupus eythematosus in pregnancy. *Lancet* **338**: 756–757

Tindall RSA, Walker JE, Ehle AL *et al* 1982 Plasmapheresis in multiple sclerosis: prospective trial of pheresis and immunosuppression versus immunosuppression alone. *Neurology* **32**: 739–743

Tintoré M, Rovira A, Martinez MJ *et al* 2000 Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. *Am J Neuroradiol* **21**: 702–706

Tintoré M, Rovira A, Brieva L *et al* 2001 Isolated demyelinating syndromes: comparison of CSF oligoclonal bands and different imaging criteria to predict conversion to CDMS. *Mult Scler* **7**: 359–363

Tintoré M, Rovira A, Rio J *et al* 2003 New diagnostic criteria for multiple sclerosis: application in first demyelinating episode. *Neurology* **60**: 27–30

Tintoré M, Rovira A, Rio J *et al* 2005 Is optic neuritis more benign than other first attacks in multiple sclerosis? *Ann Neurol* **57**: 210–215

Tippett DS, Fishman PS, Panitch HS 1991 Relapsing transverse myelitis. *Neurology* **41**: 703–706

Tisch R, Yang Y-D, Singer SM *et al* 1993 Immune response to glutamic acid decarboxylase correlates with insulitis in non-obese diabetic mice. *Nature* **366**: 72–75

Titcombe AF, Willison RG 1961 Flicker fusion in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **24**: 260–265

Tivol EA, Borriello F, Schweitzer AN *et al* 1995 Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity* **3**: 541–547

Tjoa CW, Benedict RH, Winstock-Guttman B *et al* 2005 MRI T2 hypointensity of the dentate nucleus is related to ambulatory impairment in multiple sclerosis. *J Neurol Sci* **234**: 17–24

Todman DH 1988 A paroxysmal ocular motility disorder in multiple sclerosis. *Aust NZ J Med* **18**: 785–787

Toivanen AL, Valanne L, Tatlisumak T 2002 Acute disseminated encephalomyelitis following nephropathia epidemica. *Acta Neurol Scand* **105**: 333–336

Tola MA, Yugueros MI, Fernandez-Buey N, Fernandez-Herranz R 1999 Prevalence of multiple sclerosis in Valladolid, Spain. *J Neurol* **246**: 170–174

Tola MR, Granieri E, Caniatti L *et al* 1992 Systemic lupus erythematosus presenting with neurological disorders. *J Neurol* **239**: 61–64

Toma JG, Akhavan M, Fernandus KJ *et al* 2001 Isolation of multipotent adult stem cells from dermis of mammalian skin. *Nat Cell Biol* **3**: 778–784

Toms R, Weiner HL, Johnson D 1990 Identification of IgE-positive cells and mast cells in frozen sections of multiple sclerosis brains. *J Neuroimmunol* **30**: 169–177

Tonegawa S 1983 Somatic generation of antibody diversity. *Nature* **302**: 575–581

Toosy AT, Werring DJ, Bullmore ET *et al* 2002 Functional magnetic resonance imaging of the cortical response to photic stimulation in humans following optic neuritis recovery. *Neurosci Lett* **330**: 255–259

Toosy AT, Hickman SJ, Miszkiel KA *et al* 2005 Adaptive cortical plasticity in higher visual areas after acute optic neuritis. *Ann Neurol* **57:** 622–633

Tooyama I, Kimura H, Akiyama H, McGeer PL 1990 Reactive microglia express class I and class II major histocompatibility complex antigens in Alzheimer's disease. *Brain Res* **523**: 273–280

Topaloglu H, Berker M, Kansu T *et al* 1992 Optic neuritis and myelitis after booster tetanus toxoid vaccination. *Lancet* **339**: 178–179

Torrey EF, Miller J, Rawlings R, Yolken RH 2000 Seasonal birth patterns of neurological disorders. *Neuroepidemiology* **19**: 177–185

Tosti ME, Traversa G, Bianco E, Mele A 1999 Multiple sclerosis and vaccination against hepatitis B: analysis of risk benefit profile. *Ital J Gastroenterol Hepatol* **31**: 388–391

Totaro R, Marini C, Cialfi A *et al* 2000 Prevalence of multiple sclerosis in the L'Aquila district, central Italy. *J Neurol Neurosurg Psychiatry* **68**: 349–352

Totoiu MO, Nistor GI, Lane TE, Keirstead HS 2004 Remyelination, axonal sparing, and locomotor recovery following transplantation of glial-committed progenitor cells into the MHV model of multiple sclerosis. *Exp Neurol* **187**: 254–265

Tourbah A, Gout O, Liblau R *et al* 1999 Encephalitis after hepatitis B vaccination: recurrent disseminated encephalitis or MS? *Neurology* **53**: 396–401

de la Tourette G 1886 *Etudes cliniques et physiologiques sur la marché*. Paris: Progrès Médicale and Delahaye et Lecrosnier

Tournier-Lasserve E, Cashman N, Roullet E, Lyoncean O, Degos JD, Bach MA 1987 T-cell markers in cerebrospinal fluid of patients with multiple sclerosis and other neurological diseases. In: Lowenthal A, Raus J (eds) *Cellular and Humoral Immunological Components of Cerebrospinal Fluid in Multiple Sclerosis*. New York: Plenum Press, pp. 237–248

Tourtellotte WW 1985 The cerebrospinal fluid in multiple sclerosis. *Handbook of Clinical Neurology, Vol 3*. Amsterdam: Elsevier, pp. 79–130

Tourtellotte WW, Parker JA 1966 Multiple sclerosis: correlation between immunoglobulin G in cerebrospinal fluid and brain. *Science* **154**: 1044–1046

Tourtellotte WW, Potvin AR, Baumhefner RW *et al* 1980 Multiple sclerosis de novo CNS IgG synthesis. *Arch Neurol* **37**: 620–624

Tourtellotte WW, Baumhefner RW, Syndulko K *et al* 1988 The long march of the cerebrospinal fluid profile indicative of clinical definite multiple sclerosis; and still marching. *J Neuroimmunol* **20**: 217–227

Touzé E, Gout O, Verdier-Taillefer MH *et al* 2000 Premier épisode de démyélinisation du système nerveux central et vaccination contre l'hépatite B. Etude cas-témoins pilote *Rev Neurol* **156**: 242–246

Touzé E, Fourrier A, Rue-Fenouche C *et al* 2002 Hepatitis B vaccination and first central nervous system demyelinating event: a case-control study. *Neuroepidemiology* **21**: 180–186

Toyonaga B, Yoshikai Y, Vadasz V *et al* 1985 Organisation and sequences of the diversity, joining and constant regions of the human T cell receptor beta chain. *Proc Natl Acad Sci USA* **82**: 8624–8628

Trabattoni D, Ferrante P, Fusi ML *et al* 2000 Augmented type 1 cytokines and human endogenous retroviruses specific immune responses in patients with acute multiple sclerosis. *J Neurovirol* **6**: S38–S41

Traboulsee A, Dehmeshki J, Brex PA *et al* 2002 Normal-appearing brain tissue MTR histograms in clinically isolated syndromes suggestive of MS. *Neurology* **59**: 126–128

Traboulsee A, Dehmeshki J, Peters KR *et al* 2003 Disability in multiple sclerosis is related to normal appearing brain tissue MTR histogram abnormalities. *Mult Scler* **9**: 566–573

Traccis S, Rosati G, Monaco M, Aiello I, Agnetti V 1990 Successful treatment of acquired pendular elliptical nystagmus in multiple sclerosis with isoniazid and base-out prisms. *Neurology* **40**: 492–494

Tran EH, Hoekstra K, Van Rooijen N *et al* 1998 Immune invasion of the central nervous system parenchyma and experimental allergic encephalomyelitis, but not leukocyte extravasation from blood, are prevented in macrophage-depleted mice. *J Immunol* **161**: 3767–3775

Tran EH, Prince EN, Owens T 2000a IFN-gamma shapes immune invasion of the central nervous system via regulation of chemokines. *J Immunol* **164**: 2759–2768

Tran EH, Kuziel WA, Owens T 2000b Induction of experimental autoimmune encephalomyelitis in C57BL/6 mice deficient in either the chemokine macrophage inflammatory protein-1alpha or its CCR5 receptor. *Eur J Immunol* **30**: 1410–1415

Tran GT, Hodgkinson SJ, Carter N *et al* 2002 Attenuation of experimental allergic encephalomyelitis in complement component 6-deficient rats is associated with reduced complement C9 deposition, P-selectin expression, and cellular infiltrate in spinal cords. *J Immunol* **168**: 4293–4300

Tran M, Bhargava R, MacDonald IM 2001 Leber hereditary optic neuropathy, progressive visual loss, and multiple-sclerosis-like symptoms. *Am J Ophthalmol* **132**: 591–593

Tranchant C, Bhatia KP, Marsden CD 1995 Movement disorders in multiple sclerosis. *Mov Disord* **10**: 418–423

Transatlantic Multiple Sclerosis Genetics Cooperative 2001 A meta-analysis of genome screens in multiple sclerosis. *Mult Scler* **7**: 3–11

Transverse Myelitis Consortium Working Group 2002 Proposed diagnostic criteria and nosology of acute transverse myelitis. *Neurology* **59**: 499–505

Trapp BD 2004 Pathogenesis of multiple sclerosis: the eyes only see what the mind is prepared to comprehend. *Ann Neurol* **55**: 455–457

Trapp BD, Peterson J, Ransohof RM *et al* 1998 Axonal transection in the lesions of multiple sclerosis. *N Engl J Med* **338**: 278–285

Trapp BD, Ransohoff R, Rudick R 1999 Axonal pathology in multiple sclerosis: relationship to neurologic disability. *Curr Opin Neurol* **12**: 295–302

Traugott U, Lebon P 1988a Multiple sclerosis: involvement of interferons in lesion pathogenesis. *Ann Neurol* **24**: 243–251

Traugott U, Lebon P 1988b Demonstration of alpha, beta, and gamma interferon in active chronic multiple sclerosis lesions. *Ann NY Acad Sci* **540**: 309–311

Traugott U, Lebon P 1988c Interferon-γ and Ia antigen are present on astrocytes in active chronic multiple sclerosis lesions. *J Neurol Sci* **84**: 257–264

Traugott U, Reinherz EL, Raine CS 1983a Multiple sclerosis: distribution of T cells, T cell subsets and Ia-positive macrophages in lesions of different ages. *J Neuroimmunol* **4**: 201–221

Traugott U, Reinherz EL, Raine CS 1983b Multiple sclerosis: distribution of T cell subsets within active chronic lesions. *Science* **219**: 308–310

Trebst C, Sorensen TL, Kivisäkk P *et al* 2001 CCR1+/CCR5+ mononuclear phagocytes accumulate in the central nervous system of patients with multiple sclerosis. *Am J Pathol* **159**: 1701–1710

Treib J, Haas A, Stille W *et al* 2000 Multiple sclerosis and *Chlamydia pneumoniae*. *Ann Neurol* **47**: 408

Tremlett HL, Luscombe DK, Wiles CM 1998 Use of corticosteroids in multiple sclerosis by consultant neurologists in the United Kingdom. *J Neurol Neurosurg Psychiatry* **65**: 362–365

Trevisani F, Gattinara GC, Caraceni P *et al* 1993 Transverse myelitis following hepatitis B vaccination. *J Hepatol* **19**: 317–318

Trinchieri G 2003 Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nature Rev Immunol* **3**: 133–146

Trinka E, Unterberger I, Spiegel M *et al* 2002 De novo aphasic status epilepticus as presenting symptom of multiple sclerosis. *J Neurol* **249**: 782–783

Trip SA, Schlottmann P, Jones SJ *et al* 2005 Retinal nerve fibre layer axonal loss and visual dysfunction in optic neuritis. *Ann Neurol* **58**: 383–391

Tröhler U 2000 *To Improve the Evidence of Medicine. The eighteenth-century British origins of a critical approach*. Edinburgh: Royal College of Physicians

Troiano R, Hafstein M, Ruderman M *et al* 1984 Effect of high-dose intravenous steroid administration on contrast-enhancing computed tomographic scan lesions in multiple sclerosis. *Ann Neurol* **15**: 257–263

Troiano R, Jotkowitz A, Cook SD *et al* 1992 Rate and types of fractures in corticosteroid-treated multiple sclerosis patients. *Neurology* **42**: 1389–1391

Trojaborg W, Petersen E 1979 Visual and somatosensory evoked cortical potentials in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **42**: 323–330

Trojano M, Avolio C, Manzari C *et al* 1995 Multivariate analysis of predictive factors of multiple sclerosis with a validated method to assess clinical events. *J Neurol Neurosurg Psychiatry* **58**: 300–306

Trojano M, Avolio C, Simone IL *et al* 1996 Soluble intercellular adhesion molecule 1 in serum and cerebrospinal fluid of clinically active relapsing–remitting multiple sclerosis: correlation with Gd-TPA magnetic resonance imaging-enhancement and cerebrospinal fluid findings. *Neurology* **47**: 1535–1541

Trojano M, Liguori M, De Robertis F *et al* 1999 Comparison of clinical and demographic features between affected pairs of Italian multiple sclerosis multiplex families; relation to tumour necrosis factor genomic polymorphisms. *J Neurol Sci* **162**: 194–200

Trojano M, Liguori M, Zimatore GB *et al* 2002 Age-related disability in multiple sclerosis. *Ann Neurol* **51**: 475–480

Trooster WJ, Teelken AW, Kampinga J *et al* 1993 Suppression of acute experimental allergic encephalomyelitis by the synthetic sex hormone 17-alpha-ethinylestradiol: an immunological study in the Lewis rat. *Int Arch Allergy Immunol* **102**: 133–140

Trooster WJ, Teelken AW, Lijnema TH *et al* 1994 Treatment of acute experimental allergic encephalomyelitis in the Lewis rat with the sex hormone progesterone. *Int J Immunopath Pharmacol* **7**: 183–192

Trostle DC, Helfrich D, Medsger TA 1986 Systemic sclerosis (scleroderma) and multiple sclerosis. *Arthritis Rheum* **29**: 124–127

Trotter J, Schachner M 1989 Cells positive for the 04 surface antigen isolated by cell sorting are able to differentiate into astrocytes or oligodendrocytes. *Dev Brain Res* **46**: 115–122

Trotter JL, Garvey WF 1980 Prolonged effects of large-dose methylprednisolone infusion in multiple sclerosis. *Neurology* **30**: 702–708

Trouillas P, Courjon L 1972 Epilepsy with multiple sclerosis. *Epilepsia* **13**: 325–333

Trousse F, Giess MC, Soula C *et al* 1995 Notochord and floor plate stimulate oligodendrocyte differentiation in cultures of the chick dorsal neural tube. *J Neurosci Res* **41**: 552–560

Trowsdale J, Hanson I, Mockridge I *et al* 1990 Sequences encoded in the class II region of the MHC related to the ABC superfamily of transporters. *Nature* **348**: 741–744

Trubo R 2001 *Courage. The story of the mighty effort to end the devastating effects of multiple sclerosis*, Chicago: Ivan Dee

Truelle JL, Pallison E, LeGall D *et al* 1987 Troubles intellectuels et thymiques dans la sclérose en plaques. *Rev Neurol* **143**: 595–601

Truyen L, van Waesberghe JHTM, van Walderveen MAA et al 1996 Accumulation of hypointense lesion ('black holes') on T1 SE MRI in multiple sclerosis correlates with disease progression. *Neurology* **47**: 1469–1476

Tsai CP, Yuan CL, Yu HY *et al* 2004 Multiple sclerosis in Taiwan. *J Chin Med Assoc* **67**: 500–505

Tsai HH, Frost E, To V *et al* 2002 The chemokine receptor CXCR2 controls positioning of oligodendrocyte precursors in developing spinal cord by arresting their migration. *Cell* **110**: 373–383

Tsai HH, Tessier-Lavigne M, Miller RH 2003 Netrin 1 mediates spinal cord oligodendrocyte precursor dispersal. *Development* **130**: 2095–2105

Tschabitscher H 1958 Die klinïschen und experimentellen Forschungen der multiplen Sklerose. *Wiener Z Nervenheilk* **14**: 381

Tselis A 2001 Acute disseminated encephalomyelitis. *Curr Treat Options Neurol* **3**: 537–542

Tselis AC, Lisak RP 1995 Acute disseminated encephalomyelitis and isolated central nervous system demyelinative syndromes. *Curr Opin Neurol* **8**: 227–229

Tsuchida T, Parker KC, Turner RV *et al* 1995 Autoreactive $CD8^+$ T cell responses to human myelin protein-derived peptides. *Proc Natl Acad Sci USA* **91**: 10859–10863

Tsukada N, Miyagi K, Matsuda M *et al* 1991 Tumor necrosis factor and interleukin-1 in the CSF and sera of patients with multiple sclerosis. *J Neurol Sci* **104**: 230–234

Tsukada N, Matsuda M, Miyagi K, Yanagisawa N 1993 Increased levels of intercellular adhesion molecule-1 (ICAM-1) and tumor necrosis factor receptor in the cerebrospinal fluid of patients with multiple sclerosis. *Neurology* **43**: 2679–2682

Tsukada N, Matsuda M, Miyagi K, Yanagisawa N 1994 *In vitro* intercellular adhesion molecule-1 expression on brain endothelial cells in multiple sclerosis. *J Neuroimmunol* **49**: 181–187

Tsukada N, Miyagi K, Matsuda M, Yanagisawa N 1995 Soluble E-selectin in the serum and cerebrospinal fluid of patients with multiple sclerosis and human T-lymphocyte virus type 1-associated myelopathy. *Neurology* **45**: 1914–1918

Tsunoda I, Kuang LQ, Theil DJ, Fujinami RS 2000 Antibody association with a novel model for primary progressive multiple sclerosis: induction of relapsing–remitting and progressive forms of EAE in H2s mouse strains. *Brain Pathol* **10**: 402–418

Tubridy N, Ader HJ, Barkhof F *et al* 1998a Exploratory treatment trials in multiple sclerosis using MRI: sample size calculations for relapsing remitting and secondary progressive subgroups using placebo controlled parallel groups. *J Neurol Neurosurg Psychiatry* **64**: 50–55

Tubridy N, Coles AJ, Molyneux P *et al* 1998b Secondary progressive multiple sclerosis: the relationship between short-term MRI activity and clinical features. *Brain* **121**: 225–231

Tubridy N, Behan PO, Capildeo R *et al* 1999 The effect of anti-alpha4 integrin antibody on brain lesion activity in MS. The UK Antegren Study Group. *Neurology* **53**: 466–472

Tuke PW, Hawke S, Griffiths PD, Clark DA 2004 Distribution and quantification of human herpesvirus 6 in multiple sclerosis and control brains. *Mult Scler* **10**: 355–359

Tullman MJ, Delman BN, Lublin FD, Weinberger J 2003 Magnetic resonance imaging in early disseminated Lyme disease. *J Neuroimaging* **13**: 264–268

Tuohy VK, Yu M, Yin L *et al* 1998 The epitope spreading cascade during experimental autoimmune encephalomyelitis and multiple sclerosis. *Immunol Rev* **164**: 93–100

Tuohy VK, Yu M, Yin L *et al* 2000 Modulation of the IL-10/IL-12 cytokine circuit by interferon-beta inhibits the development of epitope spreading and disease progression in murine autoimmune encephalomyelitis. *J Neuroimmunol* **111**: 55–63

Turnley AM, Faux CH, Rietze RL *et al* 2002 Suppressor of cytokine signaling 2 regulates neuronal differentiation by inhibiting growth hormone signaling. *Nat Neurosci* **5**: 1155–1162

Tuzun E, Akman-Demir G, Eraksoy M 2001 Paroxysmal attacks in multiple sclerosis. *Mult Scler* **7**: 402–404

Tuzun S, Altintas A, Karacan I *et al* 2003 Bone status in multiple sclerosis: beyond corticosteroids. *Mult Scler* **9**: 600–604

Tweedy HC 1894 Note on a case of insular sclerosis. *Dublin J Med Sci* **98**: 10–13

Twomey JA, Espir MLE 1980 Paroxysmal symptoms as the first manifestation of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **43**: 269–304

Tyler KL, Gross RA, Cascino GD 1986 Unusual viral causes of transverse myelitis: hepatitis A virus and cytomegalovirus. *Neurology* **36**: 855–858

Tyndall A, Koike T 2002 High-dose immunoablative therapy with hematopoietic stem cell support in the treatment of severe autoimmune disease: current status and future direction. *Intern Med* **41**: 608–612

Ubogu EE, Lindenberg JR, Werz MA 2003 Transverse myelitis associated with *Acinetobacter baumanii* intrathecal pump catheter-related infection. *Reg Anesth Pain Med* **28**: 470–474

Uccelli M, Mohr LM, Battaglia M *et al* 2004 Peer support groups in multiple sclerosis: current effectiveness and future directions. *Mult Scler* **10**: 80–84

Uchimura I, Shiraki H 1957 A contribution to the classification and pathogenesis of demyelinating encephalomyelitis. *J Neuropathol Exp Neurol* **16**: 139–208

Ueda H, Howson JMM, Esposito L *et al* 2003 Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* **423**: 506–511

Ueda N, Yoshikawa T, Chihara M *et al* 1988 Atrial fibrillation following methylprednisolone pulse therapy. *Pediatr Nephrol* **2**: 29–31

Ueno M, Tokunaga Y, Terachi S *et al* 2000 Asymmetric sweating in a child with multiple sclerosis. *Pediatr Neurol* **23**: 74–76

Uhlenbrock D, Sehlen S 1989 The value of T1-weighted images in the differentiation between MS, white matter lesions and subcortical arteriosclerotic encephalopathy (SAE). *Neuroradiology* **31**: 203–212

Uhthoff W 1890 Untersuchungen über die bei der multiplen Herdsklerose vorkommenden Augenstörungen. *Arch Psychiatr Nervenkrankeiten* **21**: 55–116

Uitdehaag BMJ, Polman CH, Valk J, Koetsier JC, Lucas CJ 1989 Magnetic resonance imaging studies in multiple sclerosis twins. *J Neurol Psychiatry* **52**:1417–1419

Uitdehaag BMJ, Ader HJ, Roosma TJA *et al* 2002 Multiple sclerosis functional composite: impact of reference population and interpretation of change. *Mult Scler* **8**: 366–371

Uitdehaag BMJ, Kappos L, Bauer L *et al* 2005 Discrepancies in the interpretation of clinical symptoms and signs in the diagnosis of multiple sclerosis. A proposal for standardization. *Mult Scler* **11**: 227–231

Uitti RJ, Rajput AH 1986 Multiple sclerosis presenting as isolated oculomotor palsy. *Can J Neurol Sci* **13**: 270–272

Uldry PA, Regli F 1992 Syndrome pseudo-radiculaire au cours de la sclérose en plaques: quartre cas avec imagerie par résonance magnétique. *Rev Neurol* **148**: 692–695

Ulrich J, Groebke-Lorenz W 1983 The optic nerve in multiple sclerosis: a morphological study with retrospective clinico-pathological correlations. *Neuroophthalmology* **3**: 149–159

Ulvestad E, Williams K, Vedeler C *et al* 1994 Reactive microglia in multiple sclerosis lesions have an increased expression of receptors for the Fc part of IgG. *J Neurol Sci* **121**: 125–131

Uncini A, Di Muzio A, Di Guglielmo G *et al* 1999 Effect of rhTNF-alpha injection into rat sciatic nerve. *J Neuroimmunol* **94**: 88–94

United Kingdom Tizanidine Trial Group 1994 A double-blind, placebo-controlled trial of tizanidine in the treatment of spasticity caused by multiple sclerosis. *Neurology* **44 (Suppl 9)**: S70–S78

Urban JL, Kumar V, Kono DH *et al* 1988 Restricted use of T cell receptor V genes in murine autoimmune encephalomyelitis raises possibilities for antibody therapy. *Cell* **54**: 577–592

Ure DR, Rodriguez M 2002 Polyreactive antibodies to glatiramer acetate promote myelin repair in murine model of demyelinating disease. *FASEB J* **16**: 1260–1262

Urenjak J, Williams SR, Gadian DG, Noble M 1993 Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. *J Neurosci* **13**: 981–989

Uria DF, Gutierrez V, Menes BB *et al* 1993 HLA class 2 susceptibility and resistance genes in patients with multiple sclerosis from northern Spain, by DNA-RFLP genotyping. *J Neurol Neurosurg Psychiatry* **56**: 722–723

Uria DF, Abad P, Calatayud MT *et al* 1997 Multiple sclerosis in Gijon health district,

Asturias, northern Spain *Acta Neurol Scand* **96**: 375–379
Us O, Lolli F, Baig S, Link H 1989 Intrathecal synthesis of beta-2-microglobulin in multiple sclerosis and aseptic meningoencephalitis. *Acta Neurol Scand* **80**: 598–602
Utz U, Biddison WE, McFarland HF *et al* 1993 Skewed T-cell receptor repertoire in genetically identical twins correlates with multiple sclerosis. *Nature* **364**: 243–247
Utzschneider DA, Thio C, Sontheimer H *et al* 1993 Action potential conduction and sodium channel content in the optic nerve of the myelin-deficient rat. *Proc R Soc Lond B* **254**: 245–250
Utzschneider DA, Archer DR, Kocsis JD *et al* 1994 Transplantation of glial cells enhances action potential conduction of amyelinated spinal cord axons in the myelin-deficient rat. *Proc Natl Acad Sci USA* **91**: 53–57
Vagg R, Mogyoros I, Kiernan MC, Burke D 1998 Activity-dependent hyperpolarization of human motor axons produced by natural activity. *J Physiol* **507**: 919–925
Vahtera T, Haaranen M, Viramo-Koskela AL, Ruutiainen J 1997 Pelvic floor rehabilitation is effective in patients with multiple sclerosis. *Clin Rehab* **11**: 211–219
Vajkoczy P, Laschinger M, Engelhardt B 2001 α4-integrin-VCAM binding mediates G protein independent capture of encephalitogenic T cell blasts to CNS white matter microvessels. *J Clin Invest* **108**: 557–565
Valdo P, Stegagno C, Mazzucco S *et al* 2003 Enhanced expression of NGF receptors in multiple sclerosis lesions. *J Neuropathol Exp Neurol* **61**: 91–98
Valentiner W 1856 Über die sklerose des Gehirns und Ruckenmarks. *Dtsch Klin* **8**: 147–151, 158–162, 167–169
Valiquette G, Adams GM, Herbert J 1992 DDAVP in the management of nocturia in multiple sclerosis. *Ann Neurol* **31**: 577
Valiquette G, Herbert J, Maede-D'Alisera P 1996 Desmopressin in the management of nocturia in patients with multiple sclerosis: a double-blind, crossover trial. *Arch Neurol* **53**: 1270–1275
Valli A, Sette A, Kappos L *et al* 1993 Binding of myelin basic protein peptides to human histocompatibility leukocyte antigen class II molecules and their recognition by T cells from multiple sclerosis patients. *J Clin Invest* **91**: 616–628
Van Assche G, Van Ranst M, Sciot R *et al* 2005 Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 353: 362–368
Vandenbark AA, Offner H, Reshef T *et al* 1985 Specificity of T lymphocyte lines for peptides of myelin basic protein. *J Immunol* **139**: 229–233
Vandenbark AA, Hashim G, Offner H 1989 Immunization with a synthetic T-cell receptor V-region peptide protects against experimental autoimmune encephalomyelitis. *Nature* **341**: 541–544
Vandenbark AA, Chou YK, Whitham R *et al* 1996a Treatment of multiple sclerosis with T-cell receptor peptides: results of a double-blind pilot trial. *Nature Med* **2**: 1109–1115
Vandenbark AA, Hashim GA, Offner H 1996b T cell receptor peptides in treatment of autoimmune disease: rationale and potential. *J Neurosci Res* **43**: 391–402
Vandenbark AA, Morgan E, Bartholomew R *et al* 2001 TCR peptide therapy in human autoimmune diseases. *Neurochem Res* **26**: 713–730
Vandenbroeck K, Martino G, Marrosu MG *et al* 1997 Occurrence and clinical relevance of an interleukin-4 gene polymorphism in patients with multiple sclerosis. *J Neuroimmunol* **76**: 189–192
Vandenbroeck K, Goris A, Murru R *et al* 1999 A dinucleotide repeat polymorphism located in the IFNalpha/beta chain cluster at chromosome 9p22 is not associated with multiple sclerosis in Sardinia. *Exp Clin Immunogenet* **16**: 26–29
Vandenbroeck K, Fiten P, Ronsse I *et al* 2000a High-resolution analysis of IL6 minisatellite polymorphism in Sardinian multiple sclerosis: effect on onset and course of disease. *Genes Immun* **1**: 460–463
Vandenbroeck K, Hardt C, Louage J *et al* 2000b Lack of association between the interferon regulatory factor-1 (IRF1) locus at 5q31.1 and multiple sclerosis in Germany, northern Italy, Sardinia and Sweden. *Genes Immun* **1**: 290–294
Vandenbroeck K, Fiten P, Heggarty S *et al* 2002 Chromosome 7q21–22 and multiple sclerosis: evidence for a genetic susceptibility effect in vicinity to the protachykinin-1 gene. *J Neuroimmunol* **125**: 141–148
Van den Burg W, van Zomeren EA, Minderhoud JM *et al* 1987 Cognitive impairment in patients with multiple sclerosis and mild physical disability. *Arch Neurol* **44**: 494–501
Van der Aa A, Hellings N, Bernard CCA *et al* 2003 Functional properties of myelin oligodendrocyte glycoprotein-reactive T cells in multiple sclerosis patients and controls. *J Neuroimmunol* **137**: 164–176
Van der Knaap MS, van der Voorn P, Barkhof F *et al* 2003 A new leukodystrophy with brainstem and spinal cord involvement and high lactate. *Ann Neurol* **53**: 252–258
Vanderlugt CL, Miller SD 2002 Epitope spreading in immunemediated diseases: implications for immunotherapy. *Nature Rev Immunol* **2**: 85–95
Vanderlugt CL, Karandikar NJ, Lenschow DJ *et al* 1997 Treatment with intact anti-B7–1 mAb during disease remission enhances epitopes spreading and exacerbates relapses in R-EAE. *J Neuroimmunol* **79**: 113–118
Vandevyver C, Stinissen P, Cassiman J-J, Raus J 1994a TAP1 and TAP2 transporter gene polymorphisms in multiple sclerosis: no evidence for disease association with TAP. *J Neuroimmunol* **54**: 35–40
Vandevyver C, Buyse I, Philippaerts L *et al* 1994b HLA and T-cell receptor polymorphisms in Belgian multiple sclerosis patients: no evidence for disease association with the T-cell recpetor. *J Neuroimmunol* **52**: 25–32
Van Ewijk W 1991 T cell differentiation is influenced by thymic microenvironments. *Ann Rev Immunol* **9**: 591–616
Van Ewijk W, Shores EW, Singer A 1994 Crosstalk in the mouse thymus. *Immunol Today* **15**: 214–217
Vaney C, Henzel-Gutenbrunner M, Jobin P *et al* 2004 Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult Scler* **10**: 417–424
Van Geel BM, Bezman L, Loes DJ *et al* 2001 Evolution of phenotypes in adult male patients with X-linked adreno-leucodystrophy. *Ann Neurol* **49**: 186–194
Van Gehuchten P 1966 Lesions de ganglions spineaux dans la sclérose en plaques. *Acta Neurol Belg* **66**: 331–340
Van Lieshout HBM, Van Engelen BGM, Sanders EACM, Renier WA 1993 Diagnosing multiple sclerosis in childhood. *Acta Neurol Scand* 88: 339–343
Van Noort J, van Sechel AC, Bajramovic JJ *et al* 1995 The small heat-shock protein αβ crystallin as candidate autoantigen in multiple sclerosis. *Nature* **375**: 798–810
Vanopdenbosch L, Dubos B, D'Hooghe MB *et al* 2000 Mitochondrial mutations of Leber's hereditary optic neuropathy: a risk factor for multiple sclerosis. *J Neurol* **247**: 535–543
Van Waesberghe JHTM, Kamphorst W, De Groot CRA *et al* 1999 Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. *Ann Neurol* **46**: 747–754
Van Walderveen MAA, Tas MW, Barkhof F *et al* 1994 Magnetic resonance evaluation of disease activity during pregnancy in multiple sclerosis. *Neurology* **44**: 327–332
Van Walderveen MA, Barkhof F, Tas MW *et al* 1998a Patterns of brain magnetic resonance abnormalities on T2-weighted spin echo images in clinical subgroups of multiple sclerosis: a large cross-sectional study. *Eur Neurol* **40**: 91–98
Van Walderveen MAA, Kamphorst W, Scheltens P *et al* 1998b Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. *Neurology* **50**: 1282–1288
Van Walderveen MAA, Barkhof F, Pouwels PJW *et al* 1999a Neuronal damage in T1-hypointense multiple sclerosis lesions demonstrated in vivo using proton magnetic resonance spectroscopy. *Ann Neurol* **46**: 79–87
Van Walderveen MAA, Truyen L, van Oosten BW *et al* 1999b Development of hypointense lesions on T1-weighted spin-echo magnetic resonance images in multiple

sclerosis: relation to inflammatory activity. *Arch Neurol* **56**: 345–351
Vartanian T, Fischbach G, Miller R 1999 Failure of spinal cord oligodendrocyte development in mice lacking neuregulin. *Proc Natl Acad Sci USA* **96**: 731–735
Vartanian T, Sorensen PS, Rice G 2004 Impact of neutralizing antibodies on the clinical efficacy of interferon beta in multiple sclerosis. *J Neurol* **251**: II25–II30
Vartdal F, Sollid LM, Vandevik B *et al* 1989 Patients with multiple sclerosis carry DQb1 genes which encode shared polymorphic amino acid sequences. *Hum Immunol* **25**: 103–110
Vas CJ 1969 Sexual impotence and some autonomic disturbances in men with multiple sclerosis. *Acta Neurol Scand* **45**: 166–183
Vass K, Lassmann H 1990 Intrathecal application of interferon gamma: progressive appearance of MHC antigens within the rat nervous system. *Am J Pathol* **137**: 789–800
Vass K, Lassmann H, Wisniewski HM, Iqbal K 1984 Ultracytochemical distribution of myelin basic protein after injection into the cerebrospinal fluid. *J Neurol Sci* **63**: 423–433
Vass K, Lassmann H, Wekerle H, Wisniewski HM 1986 The distribution of Ia antigen in the lesions of rat acute experimental allergic encephalomyelitis. *Acta Neuropathol* **70**: 149–160
Vass K, Heininger K, Schäfer B *et al* 1992 Interferon-γ potentiates antibody-mediated demyelination *in vivo*. *Ann Neurol* **32**: 198–206
Vassallo L, Elian M, Dean G 1978 Multiple sclerosis in southern Europe. II. Prevalence in Malta in 1978. *J Epidemiol Commun Hlth* **33**: 111–113
Vaughan JH, Riise T, Rhodes GH *et al* 1996 An Epstein Barr virus-related cross reactive autoimmune response in multiple sclerosis in Norway. *J Neuroimmunol* **69**: 95–102
van Veen T, Crusius JBA, Schrijver HM *et al* 2001 Interleukin-12p40 genotype plays a role in the susceptibility to multiple sclerosis. *Ann Neurol* **50**: 275
van Veen T, Kalkers NF, Crusius JBA *et al* 2002 The FAS-670 polymorphism influences susceptibility to multiple sclerosis. *J Neuroimmunol* **128**: 95–100
van Veen T, Crusius JBA, van Winsen L *et al* 2003a CTLA-4 and CD28 gene polymorphisms in susceptibility, clinical course and progression of multiple sclerosis. *J Neuroimmunol* **140**: 188–193
van Veen T, van Winsen L, Crusius JB *et al* 2003b [Alpha]B-crystallin genotype has impact on the multiple sclerosis phenotype. *Neurology* **61**: 1245–1249
Vejjajiva A 1982 Some clinical aspects of multiple sclerosis. In: Kuroiwa Y, Kurland L (eds) *Multiple Sclerosis: East and West*. Fukoka, Japan: Kyushu University Press, pp. 117–122
Vela JM, Molina-Holgado E, Arevalo-Martin A *et al* 2002 Interleukin-1 regulates proliferation and differentiation of oligodendrocyte progenitor cells. *Mol Cell Neurosci* **20**: 489–502
Ventner JC, Adams MD, Myers EW *et al* 2001 The sequence of the human genome. *Science* **291**: 1304–1351
Verdru P, Theys P, D'Hooghe MB, Carton H 1994 Pregnancy and multiple sclerosis: the influence on long term disability. *Clin Neurol Neurosurg* **96**: 38–41
Verheul GAM, Tyssen CC 1990 Multiple sclerosis occurring with paroxysmal unilateral dystonia. *Mov Disord* **5**: 352–353
Vernant J-C, Cabre P, Smadja D *et al* 1997 Recurrent optic neuromyelitis with endocrinopathies: a new syndrome. *Neurology* **48**: 58–64
Verrips A, Nijeholt GJ, Barkhof F *et al* 1999 Spinal xanthomatosis: a variant of cerebrotendinous xanthomatosis. *Brain* **122**: 1589–1595
Ververken D, Carton H, Billiau A 1979 Intrathecal administration of interferon in MS patients. In: Karcher D, Lowenthal A, Strosberg AD (eds) *Humoral Immunology on Neurological Disease*. New York: Plenum, pp. 625–627
Vervliet G, Claeys H, van Haver H *et al* 1983 Interferon production and natural killer (NK) activity in leukocyte cultures from multiple sclerosis patients. *J Neurol Sci* **60**: 137–150
Vesalius A 1543 *De humani corporis fabrica libri septum*, Basel: Oporini
Vicari AM, Ciceri F, Folli F *et al* 1998 Acute promyelocytic leukemia following mitoxantrone as single agent for the treatment of multiple sclerosis. *Leukemia* **12**: 441–442
Vicari AP, Zlotnik A 1996 Mouse NK1.1$^+$ T cells: a new family of T cells. *Immunol Today* **17**: 71–76
Vickrey BG, Hays RD, Harooni R *et al* 1995 A health-related quality of life measure for multiple sclerosis. *Qual Life Res* **4**: 187–206
Viehover A, Miller RH, Park SK *et al* 2001 Neuregulin: an oligodendrocyte growth factor absent in active multiple sclerosis lesions. *Dev Neurosci* **23**: 377–386
Vieregge P, Klostermann W, Brückmann H 1992 Parkinsonism in multiple sclerosis. *Mov Disord* **7**: 380–382
Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA 2004 Loss of functional suppression by CD4$^+$CD25$^+$ regulatory T cells in patients with multiple sclerosis. *J Exp Med* **199**: 971–979
Vilar LM, Masjuan J, Gonzales-Porque P *et al* 2003 Intrathecal IgM synthesis is a prognostic factor in multiple sclerosis. *Ann Neurol* **53**: 222–226
Villadangos JA, Ploegh HL 2000 Proteolysis in MHC class II antigen presentation: Who's in charge? *Immunity* **12**: 233–239
Villar LM, Sádaba MC, Roldán E *et al* 2005 Intrathecal synthesis of oligoclonal IgM against myelin lipids predicts an aggressive disease course in MS. *J Clin Invest* **115**: 187–194
Villard-Mackintosh L, Vessey MP 1993 Oral contraceptives and reproductive factors in multiple sclerosis incidence. *Contraception* **47**: 161–168
Villoslada P, Barcellos LF, Rio J *et al* 2002 The HLA locus and multiple sclerosis in Spain: role in disease susceptibility, clinical course and response to interferon-B. *J Neuroimmunol* **130**: 194–201
Villoslada P, Barcellos LF, Oksenberg JR 2004 Chromosome 7q21–22 and multiple sclerosis. *J Neuroimmunol* **150**: 1–2
Vinas FC, Rengachary S 2001 Diagnosis and management of neurosarcoidosis. *J Clin Neurosci* **8**: 505–513
Vinuela FV, Fox AJ, Debrun GM *et al* 1982 New perspectives in computed tomography of multiple sclerosis. *Am J Radiol* **139**: 123–127
Vinuesa CG, Goodnow CC 2004 Illuminating autoimmune regulators through controlled variation of the mouse genome sequence. *Immunity* **20**: 669–679
Virchow R 1854 Über eine im Gehirn und Rückenmark des Menschen aufgefundene Substanz mit der chemischen Reaction der Cellulose. *Arch Pathol Anat Physiol Klin Med* **15**: 217–236
Virchow R 1858 *Cellularpathologie in ihre Begrundung auf Physiologische und Pathologische Gewebelehre*. Berlin: A. Hirschwald
Visentin S, Levi G 1997 Protein kinase C involvement in the resting and interferon-gamma-induced K$^+$ channel profile of microglial cells. *J Neurosci Res* **47**: 233–241
Visscher BR, Detels R, Dudley JP *et al* 1979 Genetic susceptibility to multiple sclerosis. *Neurology* **29**: 1354–1360
Visscher BR, Liu KS, Clark VA *et al* 1984 Onset symptoms as predictors of mortality and disability in multiple sclerosis. *Acta Neurol Scand* **70**: 321–328
Visser L, de Vos AF, Hamann J *et al* 2002 Expression of the EGF-TM7 receptor CD97 and its ligand CD55 (DAF) in multiple sclerosis. *J Neuroimmunol* **132**: 156–163
Visser LH, Beekman R, Tijssen CC *et al* 2004 A randomized, double-blind, placebo-controlled pilot study of i.v. immune globulins in combination with i.v. methylprednisolone in the treatment of relapses in patients with MS. *Mult Scler* **10**: 89–91
Vitale E, Cook S, Sun R *et al* 2002 Linkage analysis conditional on HLA status in a large North American pedigree supports the presence of a multiple sclerosis susceptibility locus on chromosome 12p12. *Hum Mol Genet* **11**: 295–300
Vitali C, Bombardieri S, Moutsopoulos HM *et al* 1996 Assessment of the European classification criteria for Sjogren's syndrome in a series of clinically defined cases: results of a prospective multicentric study. *Ann Rheum Dis* **55**: 116–121

Vitali C, Bombardieri S, Jonsson R *et al* 2002 Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the European-American Consensus Group. *Ann Rheum Dis* **61**: 554–558

Vogt MHJ, Lopatinskaya L, Smits M *et al* 2003 Elevated osteopontin levels in active relapsing–remitting multiple sclerosis. *Ann Neurol* **53**: 819–822

Vollenweider R, Lennert K 1983 Plasmacytoid T-cell clusters in non-specific lymphadenitis. *Virchows Arch B* **44**: 1–14

Vollmer TL, Key L, Durkalski V *et al* 2004a Oral simvastatin treatment in relapsing–remitting multiple sclerosis. *Lancet* **363**: 1607–1608

Vollmer TL, Phillips JT, Goodman AD *et al* 2004b An open-label safety and drug interaction study of natalizumab (Antegren™) in combination with interferon-beta (Avonex®) in patients with multiple sclerosis. *Mult Scler* **10**: 511–520

Voltz R, Starck M, Zingler V *et al* 2004 Mitoxantrone therapy in multiple sclerosis and acute leukaemia: a case report out of 644 treated patients. *Mult Scler* **10**: 472–474

Von Leden H, Horton BT 1948 The auditory nerve in multiple sclerosis. *Arch Otolaryngol* **48**: 51–57

Vorechovsky I, Kralovicova J, Tchiloian E *et al* 2001 Does 77C-G in PTPRC modify autoimmune disorders linked to major histocompatibility locus? *Nature Genet* **29**: 22–23

de Vos AF, van Meurs M, Brok HP *et al* 2002 Transfer of central nervous system autoantigens and presentation in secondary lymphoid organs. *J Immunol* **169**: 5415–5423

Vos CMP, van Haastert ES, de Groot CJA *et al* 2003 Matrix metalloproteinase-12 is expressed in phagocytotic macrophages in active multiple sclerosis lesions. *J Neuroimmunol* **138**: 106–114

Voskuhl RR, Martin R, Bergman C *et al* 1993 T helper 1 (Th1) functional phenotype of human myelin basic protein-specific T lymphocytes. *Autoimmunity* **15**: 137–143

Voskuhl RR, Goldstein AM, Simonis T *et al* 1996 DR2/DQw1 inheritance and haplotype sharing in affected siblings from multiple sclerosis families. *Ann Neurol* **39**: 804–807

Voudris KA, Vagiakou EA, Skardoutsou A 2002 Acute disseminated encephalomyelitis associated with parainfluenza virus infection in childhood. *Brain Dev* **24**: 112–114

Vrethem M, Dahle C, Ekerfeld C *et al* 1998 CD4 and CD8 lymphocyte subsets in cerebrospinal fluid and peripheral blood from patients with multiple sclerosis, meningitis and normal controls. *Acta Neurol Scand* **97**: 215–220

de Vries E 1960 *Postvaccinial Perivenous Encephalitis*. Amsterdam: Elsevier

de Vries RR, Khan M, Bernini LF *et al* 1979 Genetic control of survival in epidemics. *J Immunogenet* **6**: 271–287

Vukusic S, Confavreux C 2003a Primary and secondary progressive multiple sclerosis. *J Neurol Sci* **206**: 153–155

Vukusic S, Confavreux C 2003b Prognostic factors for progression of disability in the secondary progressive phase of multiple sclerosis. *J Neurol Sci* **206**: 135–137

Vukusic S, Hutchinson M, Hours M *et al* 2004 Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. *Brain* **127**: 1353–1360

Vulpian A 1866 Note sur la sclerose en plaques de la moelle épinière. *L'Union Med* **30**: 459–465, 475–482, 507–512, 541–548

Vyshkina T, Leist TP, Shugart YY, Kalman B 2004 CD45 (PTPRC) as a candidate gene in multiple sclerosis. *Mult Scler* **10**: 614–617

Vyshkina T, Banisor I, Shugart YY *et al* 2005a Genetic variants of Complex I in multiple sclerosis. *J Neurol Sci* **228**: 55–64

Vyshkina T, Shugart YY, Birnbaum G *et al* 2005b Association of haplotypes in the beta-chemokine locus with multiple sclerosis. *Eur J Hum Genet* **13**: 240–247

Waage A, Halstensen A, Shalaby R, Brandtzaeg P, Kierulf P, Espevik T 1989 Local production of tumor necrosis factor α, interleukin 1 and interleukin 6 in meningococcal meningitis. Relation to the inflammatory response. *J Exp Med* **170**: 1559–1568

Wada T, Kagawa T, Ivanova A *et al* 2000 Dorsal spinal cord inhibits oligodendrocyte development. *Dev Biol* **227**: 42–55

Wade DT, Makela P, Robson P *et al* 2004 Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* **10**: 434–441

Wadia NH, Bhatia K 1990 Multiple sclerosis is prevalent in the Zoroastrians (Parsis) of India. *Ann Neurol* **28**: 177–179

Wadia NH, Trikannad VS, Krishnaswamy PR 1980 Association of HLA-B12 with multiple sclerosis in India. *Tissue Antigens* **15**: 90–93

van Waesberghe JH, van Walderveen MA, Castelijns JA *et al* 1998 Patterns of lesion development in multiple sclerosis: longitudinal observations with T1-weighted spin-echo and magnetization transfer MR. *Am J Neuroradiol* **19**: 675–683

Wagner H 2001 Toll meets bacterial CpG DNA. *Immunity* **14**: 499–502

Wagner HJ, Hennig H, Jabs WT *et al* 2000 Altered prevalence and reactivity of anti-Epstein Barr virus antibodies in patients with multiple sclerosis. *Viral Immunol* **13**: 497–502

Wagner J 1956 Devic's disease. *S Afr Med J* **30**: 489–492

Waisbren BA 1982 Swine-influenza vaccine. *Ann Intern Med* **97**: 149

Wajgt A, Gorny MK, Jenek R 1983 The influence of high-dose prednisolone medication on auto-antibody specific activity and on circulating immune complex level in cerebrospinal fluid of multiple sclerosis patients. *Acta Neurol Scand* **68**: 378–385

Wakatsuki T, Miyata M, Shishido S *et al* 2000 Sjogren's syndrome with primary biliary cirrhosis, complicated by transverse myelitis and malignant lymphoma. *Intern Med* **39**: 260–265

Wakayama T, Tabar V, Rodriguez I *et al* 2001 Differentiation of embryonic stem cell lines generated from adult somatic cells by nuclear transfer. *Science* **292**: 740–742

Wakefield AJ, More LJ, Difford J, McLaughlin JE 1994 Immunohistochemical study of vascular injury in acute multiple sclerosis. *J Clin Pathol* **47**: 129–133

Waksman BH, Porter H, Lees MB, Adams RD 1954 A study of the chemical nature and components of bovine white matter effective in producing allergic encephalomyelitis in the rabbit. *J Exp Med* **100**: 451–471

Waldner H, Whitters MJ, Sobel RA *et al* 2000 Fulminant spontaneous autoimmunity of the central nervous system in mice transgenic for the myelin proteolipid protein-specific T cell receptor. *Proc Natl Acad Sci USA* **97**: 3412–3417

Walker G, Pfeilschifter J, Kunz D 1997 Mechanisms of suppression of inducible nitric-oxide synthase (iNOS) expression in Interferon (IFN)-γ-stimulated RAW 264.7 cells by dexamethasone. *J Biol Chem* **272**: 16679–16687

Walker G, Pfeilschifter J, Otten U, Kunz D 2001 Proteolytic cleavage of inducible nitric oxide synthase (iNOS) by calpain I. *Biochim Biophys Acta* **1568**: 216–224

Wallace DC, Singh G, Lott MT *et al* 1988 Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science* **242**: 486–491

Wallace VC, Cottrell DF, Brophy PJ, Fleetwood-Walker SM 2003 Focal lysolecithin-induced demyelination of peripheral afferents results in neuropathic pain behavior that is attenuated by cannabinoids. *J Neurosci* **23**: 3221–3233

Waller A 1850 Experiments on the section of glossopharyngeal and hypoglossal nerves of the frog and observations of the alternatives produced thereby in the structure of their primitive fibres. *Phil Trans R Soc Lond* **140**: 423–429

Walley T, Barton S 1995 A purchaser perspective of managing new drugs: interferon beta as a case study. *Br Med J* **311**: 796–799

Wallin MT, Page WF, Kurtzke JF 2000 Epidemiology of multiple sclerosis in US veterans. VIII. Long term survival after onset of multiple sclerosis. *Brain* **123**: 1677–1687

Wallin MT, Page WF, Kurtzke JF 2004 Multiple sclerosis in United States veterans of Vietnam era and later military service. 1. Race, sex and geography. *Ann Neurol* **55**: 65–71

Wallstrom E, Diener P, Ljungdahl A *et al* 1996 Memantine abrogates neurological deficits,

but not CNS inflammation, in Lewis rat experimental autoimmune encephalomyelitis. *J Neurol Sci* **137**: 89–96

Walsh EC, Mather KA, Schaffner SF *et al* 2003 An integrated haplotype map of the human major histocompatibility complex. *Am J Hum Genet* **73**: 580–590

Walter MA, Gibson WT, Ebers GC, Cox DW 1991 Susceptibility to multiple sclerosis is associated with the proximal immunoglobulin heavy chain region. *J Clin Invest* **87**: 1266–1273

Waltereit R, Kuker W, Jurgens S *et al* 2002 Acute transverse myelitis associated with *Coxiella burnetii* infection. *J Neurol* **249**: 1459–1461

Walther EU, Hohlfeld R 1999 Multiple sclerosis: side effects of interferon beta therapy and their management. *Neurology* **53**: 1622–1627

Wanders RJA, van Roermund CWT, van Wijland MJA *et al* 1988 X linked adrenoleukodystrophy: identification of the primary defect at the level of a deficient peroxisomal very long chain fatty acyl CoA synthetase using a newly developed method for the isolation of peroxisomes from skin fibroblasts. *J Inherited Metab Dis* **11 (Suppl 2)**: 173–177

Wandinger KP, Wessel K, Trillenberg P *et al* 1998 Effect of high-dose methylprednisolone administration on immune functions in multiple sclerosis patients. *Acta Neurol Scand* **97**: 359–365

Wandinger KP, Jabs W, Siekhaus A *et al* 2000 Association between clinical disease activity and Epstein-Barr virus reactivation in MS. *Neurology* **55**:178–184

Wandinger KP, Sturzebecher CS, Bielekova B *et al* 2001 Complex immunomodulatory effects of interferon-beta in multiple sclerosis include the upregulation of T helper 1-associated marker genes. *Ann Neurol* **50**: 349–357

Wang B, Geng Y-B, Wang C-R 2001 CD1-restricted NK T cells protect nonobese diabetic mice from developing diabetes. *J Exp Med* **194**: 313–320

Wang CY, Kawashima H, Takami T *et al* 1998 A case of multiple sclerosis with initial symptoms of narcolepsy. *No To Hattatsu* **30**: 300–306

Wang H, Allen ML, Grigg JJ *et al* 1995 Hypomyelination alters K+ channel expression in mouse mutants shiverer and trembler. *Neuron* **15**: 1337–1347

Wang KC, Koprivica V, Kim JA *et al* 2002 Oligodendrocyte-meylin glycoprotein is a Nogo receptor ligand that inhibits neurite outgrowth. *Nature* **417**: 941–944

Wang L-C, Baird DH, Hatten ME, Mason CA 1994 Astroglial differentiation is required for support of neurite outgrowth. *J Neurosci* **14**: 3195–3207

Wang S, Sdrulla AD, diSibio G *et al* 1998 Notch receptor activation inhibits oligodendrocyte differentiation. *Neuron* **21**: 63–75

Wang S, Cheng Q, Malik S, Yang J 2000 Interleukin-1beta inhibits gamma-aminobutyric acid type A (GABA(A)) receptor current in cultured hippocampal neurons. *J Pharmacol Exp Ther* **292**: 497–504

Wang S, Sdrulla A, Johnson JE *et al* 2001 A role for the helix-loop-helix protein ID2 in the control of oligodendrocyte development. *Neuron* **29**: 603–614

Wang W-Z, Olsson T, Kostulas V, Hojeberg B, Ekre H-P, Link H 1992 Myelin antigen reactive T cells in cerebrovascular diseases. *Clin Exp Immunol* **88**: 157–162

Wansen K, Pastinen T, Kuokkanen S *et al* 1997 Immune system genes in multiple sclerosis: genetic association and linkage analysis on TCR-β, IGH, IFN-γ and IL-1ra/IL-1B loci. *J Neuroimmunol* **79**: 29–36

Warf BC, Fok-Seang J, Miller RH 1991 Evidence for the ventral origin of oligodendrocyte precursors in the rat spinal cord. *J Neurosci* **11**: 2477–2488

Warren KG, Catz I, Jeffrey VM, Carrol DJ 1986 Effect of methylprednisolone on CSF IgG parameters, myelin basic protein and anti-myelin basic protein in multiple sclerosis exacerbations. *Can J Neurol Sci* **13**: 25–30

Warren KG, Catz I, Johnson E, Mielke B 1994 Anti-myelin basic protein and anti-proteolipid protein specific forms of multiple sclerosis. *Ann Neurol* **35**: 280–289

Warren KG, Catz I, Steinman L 1995 Fine specificity of the antibody-response to myelin basic protein in the central nervous system in multiple sclerosis: the minimal B-cell epitope and a model of its features. *Proc Natl Acad Sci USA* **92**: 11061–11065

Warren S, Warren KG 1982 Multiple sclerosis and diabetes mellitus: further evidence of a relationship. *Can J Neurol Sci* **9**: 415–419

Warren S, Warren KG 1992 Prevalence of multiple sclerosis in Barrhead County, Alberta, Canada. *Can J Neurol Sci* **19**: 72–75

Warren S, Warren KG 1993 Prevalence of multiple sclerosis in Westlock County, Alberta. *Neurology* **43**: 1760–1763

Warren S, Warren KG 1994 A population based study of parent gender effect in familial multiple sclerosis. *Neurology* **44 (Suppl 2)**: A194

Warren S, Greenhill S, Warren KG 1982 Emotional stress and the development of multiple sclerosis: case-control evidence of a relationship. *J Chronic Dis* **35**: 821–831

Warren S, Cockerill R, Warren KG 1991a Risk factors by onset age in multiple sclerosis. *Neuroepidemiology* **10**: 9–17

Warren S, Warren KG, Cockerill R 1991b Emotional stress and coping in multiple sclerosis (MS) exacerbations. *J Psychosom Res* **35**: 37–47

Warren S, Warren KG, Svenson LW *et al* 2003 Geographic and temporal distribution of mortality rates for multiple sclerosis in Canada, 1965–1994. *Neuroepidemiology* **22**: 75–81

Warren WR 1956 Encephalopathy due to influenza vaccine. *Arch Int Med* **97**: 803–805

Warrington AE, Pfeiffer SE 1992 Proliferation and differentiation of $O4^+$ oligodendrocytes in postnatal cerebellum: analysis in unfixed tissue slices using anti-glycolipid antibodies. *J Neurosci Res* **33**: 338–353

Warrington AE, Barbarese E, Pfeiffer SE 1993 Differential myelinogenic capacity of specific developmental stages of the oligodendrocyte lineage upon transplantation into hypomyelinating hosts. *J Neurosci Res* **34**: 1–13

Warrington AE, Asakura K, Bieber AJ *et al* 2000 Human monoclonal antibodies reactive to oligodendrocytes promote remyelination in a model of multiple sclerosis. *Proc Natl Acad Sci USA* **97**: 6820–6825

Washington R, Burton J, Todd RF *et al* 1994 Expression of immunologically relevant endothelial cell activation antigens on isolated central nervous system microvessels from patients with multiple sclerosis. *Ann Neurol* **35**: 89–97

Watanabe I, Okazaki H 1973 Virus-like structure in multiple sclerosis. *Lancet* **ii**: 569–570

Watanabe M, Hadzic T, Nishiyama A 2004 Transient upregulation of Nkx2.2 expression in oligodendrocyte lineage cells during remyelination. *Glia* **46**: 311–322

Watanabe R, Wege H, Ter Meulen V 1983 Adoptive transfer of EAE-like lesions from rats with coronavirus-induced demyelinating encephalomyelitis. *Nature* **305**: 150–151

Waterhouse J (ed.) 1976 Cancer incidence in five continents. *Int Agency Res Cancer Lyon* **3**: 456

Waterston JA, Gilligan BS 1986 Paraneoplastic optic neuritis and external ophthalmoplegia. *Aust NZ J Med* **16**: 703–704

Watkins SM, Espir M 1966 Migraine and multiple sclerosis. *J Neurol Neurosurg Psychiatry* **32**: 35–37

Watts R 2000 Musculoskeletal and systemic reactions to biological therapeutic agents. *Curr Opin Rheumatol* **12**: 49–52

Waubant E, Alize P, Tourbah A, Agid Y 2001 Paroxysmal dystonia (tonic spasm) in multiple sclerosis. *Neurology* **57**: 2320–2321

Waxman SG 1981 Clinicopathological correlations in multiple sclerosis and related diseases. *Adv Neurol* **31**: 169–182

Waxman SG 1989 Demyelination in spinal cord injury. *J Neurol Sci* **91**: 1–14

Waxman SG 1992 Demyelination in spinal cord injury and multiple sclerosis: what can we do to enhance functional recovery? *J Neurotrauma* **9**: S105–S117

Waxman SG 1995 Sodium channel blockade by antibodies: a new mechanism of neurological disease? *Ann Neurol* **37**: 421–423

Waxman SG 2001 Acquired channelopathies in nerve injury and MS. *Neurology* **56**: 1621–1627

Waxman SG 2002 Sodium channels as molecular targets in multiple sclerosis. *J Rehab Res Dev* **39**: 233–242

Waxman SG 2005a Sodium channel blockers and axonal protection in neuroinflammatory disease. *Brain* **128**: 5–6

Waxman SG 2005b Cerebellar dysfunction in multiple sclerosis: evidence for an acquired channelopathy. *Prog Brain Res* **148:** 353–365

Waxman SG, Brill MH 1978 Conduction through demyelinated plaques in multiple sclerosis: computer simulations of facilitation by short internodes. *J Neurol Neurosurg Psychiatry* **41**: 408–416

Waxman SG, Foster RE 1980 Ionic channel distribution and heterogeneity of the axon membrane in myelinated fibers. *Brain Res* **203**: 205–234

Waxman SG, Geschwind N 1983 Major morbidity related to hyperthermia in multiple sclerosis. *Ann Neurol* **13**: 348

Waxman SG, Ritchie JM 1993 Molecular dissection of the myelinated axon. *Ann Neurol* **33**: 121–136

Waxman SG, Black JA, Ransom BR, Stys PK 1994a Anoxic injury of rat optic nerve: ultrastructural evidence for coupling between Na+ influx and Ca(2+)-mediated injury in myelinated CNS axons. *Brain Res* **644**: 197–204

Waxman SG, Utzschneider DA, Kocsis JD 1994b Enhancement of action potential conduction following demyelination: experimental approaches to restoration of function in multiple sclerosis and spinal cord injury. *Prog Brain Res* **100**: 233–243

Waxman SG, Dib-Hajj S, Cummins TR, Black JA 2000 Sodium channels and their genes: dynamic expression in the normal nervous system, dysregulation in disease states. *Brain Res* **886**: 5–14

Waybright EA, Gutmann L, Chou SM 1979 Facial myokymia: pathological features. *Arch Neurol* **36**: 244–245

Weatherby SJ, Mann CLA, Davies MB *et al* 2000a Polymorphisms of apolipoprotein E: outcome and susceptibility in multiple sclerosis. *Mult Scler* **6**: 32–36

Weatherby SJ, Mann CL, Fryer AA *et al* 2000b No association between the APOE epsilon4 allele and outcome and susceptibility in primary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* **68**: 532

Weatherby SJ, Thomson W, Pepper L *et al* 2001 HLA-DRB1 and disease outcome in multiple sclerosis. *J Neurol* **248**: 304–310

Webb A, Clark P, Skepper J *et al* 1995 Guidance of oligodendrocytes and their progenitors by substratum topography. *J Cell Sci* **108**: 2747–2760

Weber A, Infante-Duarte C, Sawcer S *et al* 2003 A genome-wide German screen for linkage disequilibrium in multiple sclerosis. *J Neuroimmunol* **143**: 79–83

Weber A, Wandinger K-P, Mueller W *et al* 2004 Identification and functional characterization of a highly polymorphic region in the human TRAIL promoter in multiple sclerosis. *J Neuroimmunol* **149**: 195–201

Weber F, Rudel R, Aulkemeyer P, Brinkmeier H 2002 The endogenous pentapeptide QYNAD induces acute conduction block in the isolated rat sciatic nerve. *Neurosci Lett* **317**: 33–36

Weber H, Pfadenhauer K, Stohr M, Rosler A 2002 Central hyperacusis with phonophobia in multiple sclerosis. *Mult Scler* 8: 505–509

Weber J, Delanger T, Hannequin D *et al* 1990 Anorectal manometric anomalies in seven patients with frontal lobe brain damage. *Dig Dis Sci* **35**: 225–230

Weber JL, May PE 1989 Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. *Am J Hum Genet* **44**: 388–396

Weber MS, Starch M, Wagenpfeil S *et al* 2004 Multiple sclerosis: glatiramer acetate inhibits monocyte reactivity *in vitro* and *in vivo*. *Brain* **127**: 1370–1378

Weber P, Bartsch U, Rasband MN *et al* 1999 Mice deficient for tenascin-R display alterations of the extracellular matrix and decreased axonal conduction velocities in the CNS. *J Neurosci* **19**: 4245–4262

Webster G, Knobler R, Lublin F *et al* 1996 Cutaneous ulcerations and pustular psoriasis flare caused by recombinant interferon beta injections in patients with multiple sclerosis. *J Am Acad Dermatol* **34**: 365–367

Wechsler IS 1922 Statistics of multiple sclerosis including a study of the infantile, congenital, familial, hereditary forms and the mental and psychic symptoms. *Arch Neurol Psychiatry* 8: 59–75

Weder B, Wiedersheim P, Matter L, Steck A, Otto F 1987 Chronic progressive neurological involvement in *Borrelia burgdorferi* infection. *J Neurol* **234**: 40–43

Weese D, Roskamp D, Leach G, Zimmern P 1993 Intravesical oxybutinin chloride: experience with 42 patients. *Urology* **41**: 527–530

Wegmann TG, Lin H, Guilbert L, Mosmann TR 1993 Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today* **14**: 353–356

Wei R, Jonakait GM 1999 Neurotrophins and the anti-inflammatory agents interleukin-4 (IL-4), IL-10, IL-11, and transforming growth factor-β1 (TGF-β1) down-regulate T cell costimulatory molecules B7 and CD40 on cultured rat microglia. *J Neuroimmunol* **95**: 8–18

Wei S, Charmley P, Birchfield RI, Cancannon P 1994 Human T cell receptor V beta gene polymorphisms in multiple sclerosis. *Am J Hum Genet* **56**: 963–969

Wei TY, Baumann RJ 1999 Acute disseminated encephalomyelitis after Rocky Mountain spotted fever. *Pediatr Neurol* **21**: 503–505

Weidenheim KM, Epshteyn I, Rashbaum WK, Lyman WD 1994 Patterns of glial development in the human foetal spinal cord during the late first and second trimester. *J Neurocytol* **23**: 343–353

Weinberg AD, Wyrick G, Celnik B *et al* 1993 Lymphokine mRNA expression in the spinal cord of Lewis rats with experimental autoimmune encephalomyelitis is associated with a host recruited $CD45R^{hi}/CD4^{+}$ population during recovery. *J Neuroimmunol* **48**: 105–118

Weiner HL 2000 Oral tolerance, an active immunologic process mediated by multiple mechanisms. *J Clin Invest* **106**: 935–937

Weiner HL, Ellison GW 1983 A working protocol to be used as a guideline for trials in multiple sclerosis. *Arch Neurol* **40**: 704–710

Weiner HL, Dau PC, Khatri BO *et al* 1989 Double-blind study of true versus sham plasma exchange in patients treated with immunosuppression for acute attacks of multiple sclerosis. *Neurology* **39**: 1143–1149

Weiner HL, Mackin GA, Orav EJ *et al* 1993a Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: final report of the Northeast Cooperative Multiple Sclerosis treatment group. *Neurology* **43**: 910–918

Weiner HL, Mackin GA, Matsui M *et al* 1993b Double-blind pilot trial of oral tolerisation with myelin antigens in multiple sclerosis. *Science* **259**: 1321–1324

Weinshenker BG 1997 Natural history of multiple sclerosis in randomized clinical trials. *Int Mult Scler J* **4**: 7–11

Weinshenker BG 1999 Databases in MS research: pitfalls and promises. *Mult Scler* **5**: 206–211

Weinshenker BG, Ebers GC 1987 The natural history of multiple sclerosis. *Can J Neurol Sci* **14**: 255–261

Weinshenker BG, Rodriguez M 1995 Epidemiology of multiple sclerosis. In: Gorelick PB, Alter M (eds) *Handbook of Neuroepidemiology*. New York: Marcel Decker, pp. 533–564

Weinshenker BG, Bass B, Rice GP *et al* 1989a The natural history of multiple sclerosis: a geographically based study. 1. Clinical course and disability. *Brain* **112**: 133–146

Weinshenker BG, Bass B, Rice GP *et al* 1989b The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. *Brain* **112**: 1419–1428

Weinshenker BG, Hader W, Carriere W *et al* 1989c The influence of pregnancy on disability from multiple sclerosis: a population-based study in Middlesex County, Ontario. *Neurology* **39**: 1438–1440

Weinshenker BG, Bulman D, Carriere W *et al* 1990 A comparison of sporadic and familial multiple sclerosis. *Neurology* **40**: 1354–1358

Weinshenker BG, Rice GPA, Noseworthy JH *et al* 1991a The natural history of multiple sclerosis: a geographically based study. 3: Multivariate analysis of predictive factors and models of outcome. *Brain* **114**: 1045–1056

Weinshenker BG, Rice GPA, Noseworthy JH *et al* 1991b The natural history of multiple sclerosis: a geographically based study. 4: Applications to planning and interpretation of clinical therapeutic trials. *Brain* **114**: 1057–1067

Weinshenker BG, Bass B, Karlik S, Ebers GC, Rice GPA 1991c An open trial of OKT3 in patients with multiple sclerosis. *Neurology* **41**: 1047–1052

Weinshenker BG, Penman M, Bass B 1992 A double-blind, randomised controlled trial

of pemoline in fatigue associated with multiple sclerosis. *Neurology* **42**: 1468–1471
Weinshenker BG, Issa M, Baskerville J 1996 Long-term and short-term outcome of multiple sclerosis: a 3-year follow-up study. *Arch Neurol* **53**: 353–358
Weinshenker BG, Wingerchuk DM, Liu Q *et al* 1997 Genetic variation in the tumor necrosis factor (α) gene and the outcome of multiple sclerosis. *Neurology* **49**: 378–385
Weinshenker BG, Santrach P, Bissonet AS *et al* 1998 Major histocompatibility complex class II alleles and the course and outcome of MS: a population-based study. *Neurology* **51**: 742–747
Weinshenker BG, Hebrink D, Wingerchuk DM *et al* 1999a Genetic variants in the tumor necrosis factor receptor 1 gene in patients with MS. *Neurology* **52**: 1500–1503
Weinshenker BG, O'Brien PC, Petterson TM *et al* 1999b A randomised trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* **46**: 878–886
Weinshenker BG, Hebrink DD, Klein C *et al* 2000 Genetic variation in the B7–1 gene in patients with multiple sclerosis. *J Neuroimmunol* **105**: 184–188
Weinshenker BG, Hebrink D, Kantarci O *et al* 2001 Genetic variation in the transforming growth factor β1 gene in multiple sclerosis. *J Neuroimmunol* **120**: 138–145
Weinshilboum RM, Sladek SL 1980 Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am J Hum Genet* **32**: 651–662
Weinstein A, Schwid SI, Schiffer RB *et al* 1999 Neuropsychologic status in multiple sclerosis after treatment with glatiramer. *Arch Neurol* **56**: 319–324
Weinstock-Guttman B, Ransohoff RM *et al* 1995 The interferons: biological effects, mechanisms of action, and use in multiple sclerosis. *Ann Neurol* **37**: 7–15
Weinstock-Guttman B, Kinkel R, Cohen J *et al* 1997 Treatment of fulminant multiple sclerosis with intravenous cyclophosphamide. *Neurologist* **3**: 178–185
Weinstock-Guttman B, Jacobs LD, Brownscheidle CM *et al* 2003a Multiple sclerosis characteristics in African American patients in the New York State Multiple Sclerosis Consortium. *Mult Scler* **9**: 293–298
Weinstock-Guttman B, Badgett D, Patrick K *et al* 2003b Genomic effects of IFN-beta in multiple sclerosis patients. *J Immunol* **171**: 2694–2704
Weinstock-Guttman B, Gallagher E, Baier M *et al* 2004 Risk of bone loss in men with multiple sclerosis. *Mult Scler* **10**: 170–175
Weishaupt A, Gold R, Gaupp S *et al* 1997 Antigen therapy eliminates T cell inflammation by apoptosis: effective treatment of experimental autoimmune neuritis with recombinant myelin protein P2. *Proc Natl Acad Sci USA* **94**: 1338–1343
Weiss W, Dambrosia JM 1983 Common problems in designing therapeutic trials in multiple sclerosis. *Arch Neurol* **40**: 678–680
Weissman IL 1993 Developmental switches in the immune system. *Cell* **76**: 207–218
Weitkamp LR 1983 Multiple sclerosis susceptibility: interaction between sex and HLA. *Arch Neurol* **40**: 399–401
Wekerle H 1993 Lymphocyte traffic to the brain. In: Pardridge WM (ed.) *Cellular and Molecular Biology of the Blood–Brain Barrier*. New York: Raven Press, pp. 67–85
Wekerle H 1994 Antigen presentation by CNS glia. In: Kettenmann H, Ransom B (eds) *Neuroglial Cells*. Oxford: Oxford University Press, pp. 685–699
Wekerle H, Ketelsen U-P 1977 Intrathymic pathogenesis and dual genetic control of myasthenia gravis. *Lancet* **i**: 678–680
Wekerle H, Linington C, Lassmann H, Meyerman R 1986 Cellular immune reactivity within the CNS. *Trends Neurosci* **9**: 271–277
Wekerle H, Kojima K, Lannes-Vieira J *et al* 1994 Animal models. *Ann Neurol* **36**: S47–S53
Wekerle H, Bradl M, Linington C *et al* 1996 The shaping of the brain-specific T lymphocyte repertoire in the thymus. *Immunol Rev* **149**: 231–243
Weller M, Stevens A, Sommer N *et al* 1991 Cerebrospinal fluid interleukins, immunoglobulins, and fibronectin in neuroborreliosis. *Arch Neurol* **48**: 837–841
Weller M, Constam DB, Malipiero U, Fontana A 1994 Transforming growth factor-β2 induces apoptosis of murine T cell clones without down-regulating *bcl-2* mRNA expression. *Eur J Immunol* **24**: 1293–1300
Weller RO, Kida S, Zhang E-T 1992 Pathways of fluid drainage for the brain – morphological aspects and immunological significance in rat and man. *Brain Pathol* **2**: 277–362
Weller RO, Engelhardt B, Phillips MJ 1996 Lymphocyte targeting of the central nervous system: a review of afferent and efferent CNS immune pathways. *Brain Pathol* **6**: 275–188
Wender M, Pruchnik-Grabowska D, Hertmanowska H *et al* 1985 Epidemiology of multiple sclerosis in western Poland – a comparison between prevalence rates in 1965 and 1981. *Acta Neurol Scand* **72**: 210–217
Werner FC, Vischer TL, Wohlwend D, Zubler RH 1989 Cell surface antigen CD5 is a marker for activated human B cells. *Eur J Immunol* **19**: 1209–1213
Werner K, Bitsch A, Bunkowski S *et al* 2002 The relative number of macrophages / microglia expressing macrophage colony stimulating factor and its receptor decreases in multiple sclerosis. *Glia* **40**: 121–129
Werner P, Pitt D, Raine CS 2000 Glutamate excitotoxicity – a mechanism for axonal damage and oligodendrocyte death in multiple sclerosis? *J Neural Transmission* **60 (Suppl)**: 375–380
Werner P, Pitt P, Raine CS 2001 Multiple sclerosis: altered glutamate homeostasis in lesions correlates with oligodendrocyte and axonal damage. *Ann Neurol* **50**: 169–180
Werring DJ, Brassat D, Droogan AG *et al* 2000a The pathogenesis of lesions and normal-appearing white matter changes in multiple sclerosis: a serial diffusion MRI study *Brain* **123**: 1667–1676
Werring DJ, Bullmore ET, Toosy AT *et al* 2000b Recovery from optic neuritis is associated with a change in the distribution of cerebral response to visual stimulation: a functional magnetic resonance imaging study. *J Neurol Neurosurg Psychiatry* **68**: 441–449
Westergaard E, Brightman MW 1973 Transport of proteins across normal cerebral arterioles. *J Comp Neurol* **152**: 17–44
Westlund KB 1970 Distribution and mortality time trend of multiple sclerosis and some other diseases in Norway. *Acta Neurol Scand* **46**: 455–483
Westlund KB, Kurland LT 1953 Studies on multiple sclerosis in Winnipeg, Manitoba and New Orleans, Louisiana. I. Prevalence. Comparison between the patient groups in Winnipeg and New Orleans. *Am J Hygiene* **57**: 380–396
Whitaker JN for the Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis, National Multiple Sclerosis Society 1993 Expanded clinical trials of treatment for multiple sclerosis. *Ann Neurol* **34**: 755–756
Whitaker JN 1998 Myelin basic protein in cerebrospinal fluid and other body fluids. *Mult Scler* **4**: 16–21
Whitaker JN, Lisak RP, Bashir RM *et al* 1980 Immunoreactive myelin basic protein in the cerebrospinal fluid in neurological disorders. *Ann Neurol* **7**: 58–64
Whitaker JN, Gupta M, Smith OF 1986 Epitopes of immunoreactive myelin basic protein in human cerebrospinal fluid. *Ann Neurol* **20**: 329–336
Whitaker JN, Benveniste EN, Zhou S 1990 Cerebrospinal fluid. In: Cook SD (ed.) *Handbook of Multiple Sclerosis*. New York: Marcel Dekker, pp. 251–270
Whitaker JN, Williams PH, Layton BA *et al* 1994 Correlation of clinical features and findings on cranial magnetic resonance imaging with urinary myelin basic protein-like material in patients with multiple sclerosis. *Ann Neurol* **35**: 577–585
Whitaker JN, McFarland HF, Rudge P, Reingold SC 1995a Outcome assessment in multiple sclerosis clinical trials: a critical analysis. *Mult Scler* **1**: 37–47
Whitaker JN, Kachelhofer RD, Bradley EL *et al* 1995b Urinary myelin basic protein-like material as a correlate of the progression of multiple sclerosis. *Ann Neurol* **38**: 625–632
White AT, Wilson TE, Davis SL, Petajan JH 2000 Effect of precooling on physical performance in multiple sclerosis. *Mult Scler* **6**: 176–180
White CA, McCombe PA, Pender MP 1998 Microglia are more susceptible than macrophages to apoptosis in the central nervous system in experimental

autoimmune encephalomyelitis through a mechanism not involving Fas (CD95). *Int Immunol* **10**: 935–941
White RHR 1961 The aetiology and neurological complications of retinal vasculitis. *Brain* **84**: 601–608
Whitlock FA, Siskind MM 1980 Depression as a major symptom of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **43**: 861–865
Whitney LW, Becker KG, Tresser NJ *et al* 1999 Analysis of gene expression in multiple sclerosis lesions using cDNA microarrays. *Ann Neurol* **46**: 425–428
Whittemore SR, Sanon HR, Wood PM 1993 Concurrent isolation and characterisation of oligodendrocytes, microglia and astrocytes from adult human spinal cord. *Int J Dev Neurosci* **11**: 755–764
Whittle IR, Hooper J, Pentland B 1998 Thalamic deep-brain stimulation for movement disorders due to multiple sclerosis. *Lancet* **351**: 109–110
Whytt R 1765 *Observations on the nature, causes and cure of those disorders which have been commonly called nervous hypochondriac or hysteric to which are prefixed some remarks on the sympathy of the nerves*. London: Becket, Du Hondt & Balfour
Wiberg M, Templer DI 1994 Season of birth in multiple sclerosis in Sweden: replication of Denmark findings. *J Orthomol Med* **9**: 7–74
Wiesel PH, Norton C, Glickman S, Kamm MA 2001 Pathophysiology and management of bowel dysfunction in multiple sclerosis. *Eur J Gastroenterol Hepatol* **13**: 441–448
Wiesemann E, Klatt J, Sonmez D *et al* 2001 Glatiramer acetate (GA) induces IL-13/IL-5 secretion in naive T cells. *J Neuroimmunol* **119**: 137–144
Wiesner W, Wetzel SG, Kappos L *et al* 2002 Swallowing abnormalities in multiple sclerosis: correlation between videofluoroscopy and subjective symptoms. *Eur Radiol* **12**: 789–792
Wikstrom J, Tienari PJ, Sumelahti ML *et al* 1994 Multiple sclerosis in Finland: evidence of uneven geographic distribution, increasing frequency and high familial occurrence. In: Firnhaber W, Lauer K (eds) *Multiple Sclerosis in Europe: An Epidemiological Update*. Darmstadt: Leuchtturm-Verlag/LTV Press, pp. 73–78
Wilcox CE, Ward AMV, Evans A, Baker D, Rothlein R, Turk JL 1990 Endothelial cell expression of the intercellular adhesion molecule-1 (ICAM-1) in the central nervous system of guinea pigs during acute and chronic relapsing experimental allergic encephalomyelitis. *J Neuroimmunol* **30**: 43–50
Wilczak N, De Keyser J 1997 Insulin like growth factor-1 receptors in normal appearing white matter and chronic plaques in multiple sclerosis. *Brain Res* **772**: 243–246
Wildbaum G, Youssef S, Grabie N, Karin N 1998 Neutralizing antibodies to IFN-gamma-inducing factor prevent experimental autoimmune encephalomyelitis. *J Immunol* **161:** 6368–6374
Wildin RS, Smyk-Pearson S, Filipovich AH 2003 Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *J Med Genet* **39**: 537–545
Wiles CM, Clarke CRA, Irwin HP *et al* 1986 Hyperbaric oxygen in multiple sclerosis. *Br Med J* **292**: 367–371
Wiles CM, Omar L, Swan AV *et al* 1994 Total lymphoid irradiation in multiple sclerosis. *J Neurol Neurosurg Psychiatry* **57**: 154–163
Wiles CM, Newcombe RG, Fuller KJ *et al* 2001 Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis. *J Neurol Neurosurg Psychiatry* **70**: 174–179
Wiles CM, Brown P, Chapel H *et al* 2002 Intravenous immunoglobulin in neurological disease: a specialist review. *J Neurol Neurosurg Psychiatry* **72**: 440–448
Wiley CA, van Patten PD, Carpenter PM *et al* 1987 Acute ascending necrotising myelopathy caused by herpes simplex virus type 2. *Neurology* **37**: 1791–1794
Wilichowski E, Ohlenbusch A, Hanefeld F 1998 Characterisation of the mitochondrial genome in childhood multiple sclerosis II Multiple sclerosis without optic neuritis and LHON associated genes. *Neuropaediatrics* **29**: 307–312
Wilkin GP, Marriott DR, Cholewinski AJ 1990 Astrocyte heterogeneity. *Trends Neurosci* **13**: 43–46
Wilkins A, Compston DAS 2005 Trophic factors attenuate nitric oxide mediated neuronal and axonal injury *in vitro*: roles and interactions of MAPkinase signaling pathways. *J Neurochem* **92**: 1487–1496
Wilkins A, Chandran S, Compston A 2001 A role for oligodendrocyte-derived IGF-1 in trophic support of cortical neurons. *Glia* **36**: 48–57
Wilkins A, Majed H, Layfield R *et al* 2003 Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: a novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J Neurosci* **23**: 4967–4974
Wilks S 1878 *Lectures on Diseases of the Nervous System*. London: Churchill
Willenborg DO, Fordham SA, Cowden WB, Ramshaw IA 1995 Cytokines and murine autoimmune encephalomyelitis: inhibition or enhancement of disease with antibodies to select cytokines, or by delivery of exogenous cytokines using a recombinant vaccinia virus system. *Scand J Immunol* **41**: 31–41
Willenborg DO, Fordham SA, Bernard CC *et al* 1996 IFN-gamma plays a critical down-regulatory role in the induction and effector phase of myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. *J Immunol* **157**: 3223–3227
Willenborg DO, Staykova MA, Cowden WB 1999 Our shifting understanding of the role of nitric oxide in autoimmune encephalomyelitis: a review. *J Neuroimmunol* **100**: 21–35
Willer CJ, Sadovnick AD, Ebers GC 2002 Microchimerism in autoimmunity and transplantation: potential relevance to multiple sclerosis. *J Neuroimmunol* **126**: 126–133
Willer CJ, Dyment DA, Risch NJ *et al* 2003 Twin concordance and sibling recurrence rates in multiple sclerosis. The Canadian collaborative study. *Proc Natl Acad Sci USA* **100**: 12877–12882
Willer CJ, Dyment DA, Sadovnick AD *et al* 2005 Timing of birth and risk of multiple sclerosis: population based study. *Br Med J* **330**: 120
Williams A, Eldridge R, McFarland H *et al* 1980 Multiple sclerosis in twins. *Neurology* **30**: 1139–1147
Williams ES, McKeran RO 1986 Prevalence of multiple sclerosis in a South London borough. *Br Med J* **293**: 237–239
Williams ES, Jones DR, McKeran RO 1991 Mortality rates from multiple sclerosis: geographical and temporal variations revisited. *J Neurol Neurosurg Psychiatry* **54**: 104–109
Williams KE, Ulvestad E, Antel JP 1994 B7/BB-1 antigen expression on adult human microglia studied *in vitro* and *in situ*. *Eur J Immunol* **24**: 3031–3037
Williams MH, Bowie C 1993 Evidence of unmet need in the care of severely physically disabled adults.[retraction in BMJ. 1998 Jun 6;316(7146):1700; PMID: 9652920] *Br Med J* **306**: 95–98
Williams RM, Lees MB, Cambi F, Macklin WB 1982 Chronic allergic encephalomyelitis induced in rabbits with bovine white matter proteolipid apoprotein. *J Neuropathol Exp Neurol* 41: 508–521
Williamson RA, Burgoon MP, Owens GP *et al* 2001 Anti-DNA antibodies are a major component of the intrathecal B cell response in multiple sclerosis. *Proc Natl Acad Sci USA* **98**: 1793–1798
Williamson RT 1894 The early pathological changes in disseminated sclerosis. *Med Chronicle (Manchester)* **19**: 373–379
Williamson RT 1908 *Diseases of the Spinal Cord*. Oxford, Oxford University Press and Hodder & Stoughton
Willis T 1684 *Dr Willis's Practice of Physick*. London: Dring, Harper & Leigh
Willison HJ, Yuki N 2002 Anti-ganglioside antibodies and peripheral neuropathy. *Brain* **125**: 2591–2625
Willoughby EW, Paty DW 1988 Scales for rating impairment in multiple sclerosis: a critique. *Neurology* **38**: 1793–1798
Willoughby EW, Grochowski E, Li DKB *et al* 1989 Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. *Ann Neurol* **25**: 43–49
Wilson HC, Onischke C, Raine CS 2003 Human oligodendrocyte precursor cells in vitro: phenotypic analysis and differential response to growth factors. *Glia* **44**: 153–165

Wilson IGH 1927 Disseminated sclerosis: the rat as possible carrier of infection. *Lancet* **ii**: 1220–1223

Wilson SAK 1906 A case of disseminated sclerosis with weakness of each internal rectus and nystagmus on lateral deviation limited to the outer eye. *Brain* **29**: 297–298

Wilson SAK 1924 Pathological laughing and crying. *J Neurol Psychopathol* **4**: 299–333

Wilson SAK 1940 Disseminated sclerosis. In: *Neurology*. London: Edward Arnold, pp. 148–178

Wilson SAK, McBride HJ 1925 Epilepsy as a symptom of disseminated sclerosis. *J Neurol Psychopathology* **6**: 91–103

Wilson WA, Ghavari AE, Koike T *et al* 1999 International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum* **42**: 1309–1311

Winchester RJ, Ebers GC, Fu SM, Espinosa L, Zabriskie J, Kunkel HG 1975 B-cell allo-antigen Ag7a in multiple sclerosis. *Lancet* **ii**: 814

Windhagen A, Newcombe J, Dangond F *et al* 1995 Expression of costimulatory molecules B7–1 (CD80), B7–2 (CD86), and interleukin 12 cytokine in multiple sclerosis lesions. *J Exp Med* **182**: 1985–1986

Windhagen A, Maniak S, Marckmann S *et al* 2001 Lymphadenopathy in patients with multiple sclerosis undergoing treatment with glatiramer acetate. *J Neurol Neurosurg Psychiatry* **70**: 415–416

Windrem MS, Nunes MC, Rashbaum WK *et al* 2004 Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. *Nature Med* **10**: 93–97

Winfield JB, Shaw M, Silverman LM, Eisenberg RA, Wilson HA, Koffler D 1983 Intrathecal IgG synthesis and blood-brain barrier impairment in patients with systemic lupus erythematosus and central nervous system dysfunction. *Am J Med* **74**: 837–844

Wing MG, Zajicek JP, Seilly DJ *et al* 1992 Inhibition of antibody-dependent classical pathway activation by oligodendrocytes using CD59. *Immunology* **76**: 140–145

Wing MG, Moreau T, Greenwood J *et al* 1996 Mechanism of first-dose cytokine-release syndrome by Campath 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells. *J Clin Invest* **98**: 2819–2826

Wingerchuk DM, Weinshenker BG 2003 Neuromyelitis optica: clinical predictors of a relapsing course and survival. *Neurology* **60**: 848–853

Wingerchuk D, Liu Q, Sobell J *et al* 1997 A population-based case-control study of the tumor necrosis factor alpha-308 polymorphism in multiple sclerosis. *Neurology* **49**: 626–628

Wingerchuk DM, Benarroch E, Rodriguez M 1998 Treatment of multiple sclerosis-related fatigue with aspirin. *Can J Neurosci* **25**: S32

Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG 1999 The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* **53**: 1107–1114

Wingerchuk DM, Benarroch EE, O'Brien PC *et al* 2005 A randomized controlled crossover trial of aspirin for fatigue in multiple sclerosis. *Neurology* **64**: 1267–1269

Winter G, Milstein M 1991 Man-made antibodies. *Nature* **349**: 293–299

Winyard KE, Smith JL, Culbertson WW, Paris-Hamelin A 1989 Ocular Lyme borreliosis. *Am J Ophthalmol* **108**: 651–657

Wise CM, Agudelo CA 1988 Optic neuropathy as an initial manifestation of Sjögren's syndrome. *J Rheumatol* **15**: 799–802

Wise LH, Lanchbury JS, Lewis CM 1999 Meta-analysis of genome searches. *Ann Hum Genet* **63**: 263–272

Wisniewski HM, Lossinsky AS 1991 Structural and functional aspects of the interaction of inflammatory cells with the blood-brain barrier in experimental brain inflammation. *Brain Pathol* **1**: 89–96

Wisniewski HM, Oppenheimer D, McDonald WI 1976 Relation between myelination and function in MS and EAE. *J Neuropathol Exp Neurol* **35**: 327

Wolfson C, Confavreux C 1985 A Markov model of the natural history of multiple sclerosis. *Neuroepidemiology* **4**: 227–239

Wolfson C, Confavreux C 1987 Improvements to a simple Markov model of natural history of multiple sclerosis: I. Short term prognosis. *Neuroepidemiology* **6**: 101–115

Wolinsky JS, for the PROMiSe Study Group 2004 The PROMiSe trial: baseline data review and progress report. *Mult Scler* **10**: S65–S72

Wolinsky JS, Narayana PA, Noseworthy JH *et al* 2000 Linomide in relapsing and secondary progressive MS. Part II: MRI results. MRI Analysis Center of the University of Texas-Houston, Health Science Center, and the North American Linomide Investigators. *Neurology* **54**: 1734–1741

Wolinsky JS, Narayana PA, Johnson KP and Multiple Sclerosis Study Group and the MRI Analysis Center 2001 United States open-label glatiramer acetate extension trial for relapsing multiple sclerosis: MRI and clinical correlates. Multiple Sclerosis Study Group and the MRI Analysis Center. *Mult Scler* **7**: 33–41

Wolinsky JS, Comi G, Filippi M *et al* 2002 Copaxone's effect on MRI-monitored disease in relapsing MS is reproducible and sustained. *Neurology* **59**: 1284–1286

Wolinsky J, Pardo L, Stark Y *et al* 2003 Toward an improved understanding of primary progressive MS. *ACTRIMS 2003, Eighth Annual Meeting of the Americas Committee for Research and Treatment in Multiple Sclerosis, San Francisco, CA*, pp. 5–6

Wolswijk G 1998 Chronic stage multiple sclerosis lesions contain a relatively quiescent population of oligodendrocyte precursor cells. *J Neurosci* **18**: 601–609

Wolswijk G 2000 Oligodendrocyte survival, loss and birth in lesions of chronic-stage multiple sclerosis. *Brain* **123**: 105–115

Wolswijk G 2002 Oligodendrocyte precursor cells in the demyelinated multiple sclerosis spinal cord. *Brain* **125**: 338–349

Wolswijk G, Balesar R 2003 Changes in the expression and localization of the paranodal protein Caspr on axons in chronic multiple sclerosis. *Brain* **126**: 1638–1649

Wolswijk G, Noble M 1989 Identification of an adult specific glial progenitor cell. *Development* **105**: 387–400

Wolswijk G, Noble M 1992 Co-operation between PDGF and FGF converts slowly dividing 0–2A (adult) progenitor cells to rapidly dividing cells with characteristics of O-2A (perinatal) progenitor cells. *J Cell Biol* **118**: 889–900

Wood A, Wing MG, Benham CD, Compston DAS 1993 Specific induction of intracellular calcium oscillations by complement membrane attack on oligodendroglia. *J Neurosci* **13**: 3319–3332

Wood DD, Bilbao JM, O'Connors P, Moscarello MA 1996 Acute multiple sclerosis (Marburg type) is associated with developmentally immature myelin basic protein. *Ann Neurol* **40**: 18–24

Wood NW, Holmans P, Clayton D *et al* 1994 No linkage or association between multiple sclerosis and the myelin basic protein gene in affected sibling pairs. *J Neurol Neurosurg Psychiatry* **57**: 1191–1194

Wood NW, Kellar-Wood HF, Holmans P *et al* 1995a The T-cell receptor beta locus and susceptibility to multiple sclerosis. *Neurology* **45**: 1859–1863

Wood NW, Sawcer SJ, Kellar-Wood H *et al* 1995b A susceptibility gene for multiple sclerosis linked to the immunoglobulin heavy chain variable region. *J Neurol* **242**: 677–682

Wood PM, Bunge RP 1991 The origin of remyelinating cells in the adult central nervous system: the role of the mature oligodendrocyte. *Glia* **4**: 225–232

Wood PM, Williams AK 1984 Oligodendrocyte proliferation and CNS myelination in cultures containing dissociated embryonic neuroglia and dorsal root ganglion neurons. *Dev Brain Res* **12**: 225–241

Woodland DL 2002 Immunity and retroviral superantigens in humans. *Trends Immunol* **23**: 57–58

Woodroofe MN, Cuzner ML 1993 Cytokine mRNA expression in inflammatory multiple sclerosis lesions: detection by non-radioactive *in situ* hybridization. *Cytokine* **5**: 583–588

Woodroofe MN, Hayes GM, Cuzner ML 1989 Fc receptor density, MHC antigen expression and superoxide production are increased in interferon-γ-treated microglia isolated from adult rat brain. *Immunology* **68**: 421–426

Woodruff RH, Fruttiger M, Richardson WD, Franklin RJ 2004 Platelet-derived growth factor regulates oligodendrocyte progenitor

numbers in adult CNS and their response following CNS demyelination. *Mol Cell Neurosci* **25**: 252–262
Woods AH 1929 The nervous disease of the Chinese. *Arch Neurol Psychiatry* **21**: 542–570
Woolf CJ, Allchorne A, Safieh-Garabedian B, Poole S 1997 Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumour necrosis factor alpha. *Br J Pharmacol* **121**: 417–424
Worthington J, Jones R, Crawford M, Forti A 1994 Pregnancy and multiple sclerosis – a 3 year prospective study. *J Neurol* **241**: 228–233
Wosik K, Antel J, Kuhlmann T *et al* 2003 Oligodendrocyte injury in multiple sclerosis: a role for p53. *J Neurochem* **85**: 635–644
Wren D, Wolswijk G, Noble M 1992 *In vitro* analysis of the origin and maintenance of O-2A^{adult} progenitor cells. *J Cell Biol* **116**: 167–176
Wroe SJ, Pires M, Harding B, Youl BD, Shorvon SD 1991 Whipple's disease confined to the CNS presenting with multiple intercerebral mass lesions. *J Neurol Neurosurg Psychiatry* **54**: 989–992
Wu E, Raine CS 1992 Multiple sclerosis: interactions between oligodendrocytes and hypertrophic astrocytes and their occurrence in other, nondemyelinating conditions. *Lab Invest* **67**: 88–99
Wu E, Brosnan CF, Raine CS 1993 SP-40/40 immunoreactivity in inflammatory CNS lesions displaying astrocyte/oligodendrocyte interactions. *J Neuropathol Exp Neurol* **52**: 129–134
Wu JV, Shrager P 1994 Resolving three types of chloride channels in demyelinated Xenopus axons. *J Neurosci Res* **38**: 613–620
Wu JV, Rubinstein CT, Shrager P 1993 Single channel characterization of multiple types of potassium channels in demyelinated Xenopus axons. *J Neurosci* **13**: 5153–5163
Wu V, Schwartz JP 1998 Cell culture models for reactive gliosis: new perspectives. *J Neurosci Res* **51**: 675–681
Wucherpfennig KW 2001 Mechanisms for the induction of autoimmunity by infectious agents. *J Clin Invest* **108** 1097–1104
Wucherpfennig KW, Strominger JL 1995 Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. *Cell* **80**: 695–705
Wucherpfennig KW, Ota K, Endo N *et al* 1990 Shared human T cell receptor Vβ usage to immunodominant regions of myelin basic protein. *Science* **248**: 1016–1019
Wucherpfennig KW, Newcombe J, Li H *et al* 1992a T-cell receptor V alpha-V beta repertoire and cytokine gene expression in active multiple sclerosis lesions. *J Exp Med* **175**: 993–1002
Wucherpfennig KW, Newcombe J, Li H *et al* 1992b γδ T cell receptor repertoire in acute multiple sclerosis lesions. *Proc Natl Acad Sci USA* **89**: 4588–4592
Wucherpfennig KW, Sette A, Southwood S *et al* 1994a Structural requirements for binding of an immunodominant myelin basic protein peptide to DR2 isotypes and for its recognition by human T cells clones. *J Exp Med* **179**: 279–290
Wucherpfennig KW, Zhang J, Witek C *et al* 1994b Clonal expansion and persistence of human T cells specific for an immunodominant myelin basic protein peptide. *J Immunol* **152**: 5581–5592
Wuerfel J, Bellmann-Strobl J, Brunecker P *et al* 2004 Changes in cerebral perfusion precede plaque formation in multiple sclerosis. *Brain* **127**: 111–119
von Wussow P, von Wussow D, Jakschies HK *et al* 1990 The human intracellular Mx-homologous protein is specifically induced by type I interferons. *Eur J Immunol* **20**: 2015–2019
Wuthrich R, Rieder HP 1970 The seasonal incidence of multiple sclerosis in Switzerland. *Eur Neurol* **3**: 257–264
www.agmed.sante.gouv.fr [2004] Vaccins contre l'hépatite B: résumé des débats de la Commission Nationale de Pharmacovigilance du 21 septembre 2004
www.anaes.fr [2003] Réunion de consensus. Vaccination contre le virus de l'hépatite B. 10 et 11 septembre 2003, Paris. Texte des recommandations
www.nmss.org [2001] Research/clinical update 2 February 2001
www.who.int [2004] Global Advisory Committee on Vaccine Safety, Final Statement, September 2004
Wybar KC 1952 Ocular manifestations of disseminated sclerosis. *Proc R Soc Med* **45**: 315–320
Wynn DR, Rodriguez M, O'Fallon MM, Kurland LT 1990 A reappraisal of the epidemiology of multiple sclerosis in Olmsted County, Minnesota. *Neurology* **40**: 780–786
Wyss-Coray T, Borrow P, Brooker MJ, Mucke L 1997 Astroglial overproduction of TGF-beta 1 enhances inflammatory central nervous system disease in transgenic mice. *J Neuroimmunol* **77**: 45–50
Wyss-Coray T, Yan F, Lin AHT *et al* 2002 Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. *Proc Natl Acad Sci USA* **99**: 10837–10842
Xia MQ, Hale G, Lifely MR *et al* 1993 Structure of the Campath-1 antigen, a glycosylphosphotidylinated-anchored glycoprotein which is an exceptionally good target for complement lysis. *Biochem J* **293**: 633–640
Xiao B, Linington C, Link H 1991 Antibodies to myelin-oligodendrocyte glycoprotein in cerebrospinal fluid from patients with multiple sclerosis and controls. *J Neuroimmunol* **31**: 91–96
Xiao B, Zhang GX, Ma CG, Link H 1996 The cerebrospinal fluid from patients with multiple sclerosis promotes neuronal and oligodendrocyte damage by delayed production of nitric oxide in vitro. *J Neurol Sci* **142**: 114–120
Xin M, Yue T, Ma Z *et al* 2005 Myelinogenesis and axonal recognition by oligodendrocytes in brain are uncoupled in Olig1-null mice. *J Neurosci* **25**: 1354–1365
Xu C, Dai Y, Fredrickson S *et al* 1999 Association and linkage analysis of candidate chromosomal regions in multiple sclerosis: indication of disease genes in 12q23 and 7ptr-15. *Eur J Hum Gen* **7**: 110–116
Xu C, Dai Y, Lorentzen JC 2001 Linkage analysis in multiple sclerosis of chromosomal regions syntenic to experimental autoimmune disease loci. *Eur J Hum Gen* **9**: 458–463
Xu GY, Hughes MG, Ye Z *et al* 2004 Concentrations of glutamate released following spinal cord injury kill oligodendrocytes in the spinal cord. *Exp Neurol* **187**: 329–336
Xu X-H, McFarlin DE 1984 Oligoclonal bands in CSF: twins with MS. *Neurology* **34**: 769–774
Yabuki S, Hayabara T 1979 Paroxysmal dysesthesia in multiple sclerosis. *Folia Psychiatr Neurol Jpn* **33**: 97–104
Yahr MD, Lobo-Antunes J 1972 Relapsing encephalomyelitis following the use of influenza vaccine. *Arch Neurol* **27**: 182–183
Yamada S, DePasquale M, Patlak CS, Cserr HF 1991 Albumin outflow into deep cervical lymph from different regions of rabbit brain. *Am J Physiol* **261**: H1197–H1204
Yamamoto M 1986 Recurrent transverse myelitis associated with collagen disease. *J Neurol* **233**: 185–187
Yamamoto T, Imai T, Yamasaki M 1989 Acute ventilatory failure in multiple sclerosis. *J Neurol Sci* **89**: 313–324
Yamamoto T, Kawamura J, Hashimoto S, Nakamura M 1991 Extensive proliferation of peripheral type myelin in necrotic spinal cord lesions of multiple sclerosis. *J Neurol Sci* **102**: 163–169
Yamanouchi N, Okada S, Kodama K *et al* 1995 White matter changes caused by chronic solvent abuse. *Am J Neuroradiol* **16**: 1643–1649
Yamasaki K, Horiuchi I, Minohara M *et al* 1999 HLA-DPB1*0501-associated opticospinal multiple sclerosis: clinical, neuroimaging and immunogenetic studies. *Brain* **122**: 1689–1696
Yamashita T, Ando Y, Obayashi K *et al* 1997 Changes in nitrite and nitrate (NO2-/NO3-) levels in cerebrospinal fluid of patients with multiple sclerosis. *J Neurol Sci* **153**: 32–34
Yan H, Rivkees SA 2002 Hepatocyte growth factor stimulates the proliferation and migation of oligodendrocyte precursor cells. *J Neurosci* **69**: 597–606
Yang D, Biragyn A, Kwak LW, Oppenheim JJ 2002 Mammalian defensins in immunity: more than just microbicidal. *Trends Immunol* **23**: 291–296
Yao D-L, Webster HdeF, Hudson LD *et al* 1994 Concentric sclerosis (Balo): morphometric and *in situ* hybridization study of lesions in six patients. *Ann Neurol* **35**: 18–30

Yao D-L, Liu X, Hudson LD, Webster H deF 1995 Insulin-like growth factor 1 treatment reduces demyelination and up-regulates gene expression of myelin related proteins in experimental autoimmune encephalomyelitis. *Proc Natl Acad Sci USA* **92**: 6190–6194

Yao S, Stratton CW, Mitchell WM, Sriram S 2001 CSF oligoclonal bands in MS include antibodies against *Chlamydia* antigens. *Neurology* **56**: 1168–1176

Yapici Z, Eraksoy M 2002 Bilateral demyelinating tumefactive lesions in three children with hemiparesis. *J Child Neurol* **17**: 655–660

Yaquib BA, Daif AK 1988 Multiple sclerosis in Saudi Arabia. *Neurology* **38**: 621–623

Yarom Y, Naparstek Y, Lev-Ram V *et al* 1983 Immunospecific inhibition of nerve conduction by T lymphocytes reactive to basic protein of myelin. *Nature* **303**: 246–247

Ye P, D'Ercole AJ 1999 Insulin-like growth factor I protects oligodendrocytes from tumor necrosis factor-alpha-induced injury. *Endocrinology* **140**: 3063–3072

Ye P, Li L, Richards RG *et al* 2002 Myelination is altered in insulin-like growth factor-I null mutant mice. *J Neurosci* **22**: 6041–6051

Ye P, Bagnell R, D'Ercole AJ 2003 Mouse NG2+ oligodendrocyte precursors express mRNA for proteolipid protein but not its DM-20 variant: a study of laser microdissection-captured NG2+ cells. *J Neurosci* **23**: 4401–4405

Yednock TA, Cannon C, Fritz LC *et al* 1992 Prevention of experimental autoimmune encephalomyelitis by antibodies against α4β1 integrin. *Nature* **356**: 63–66

Yeh EA, Collins A, Cohen ME *et al* 2004 Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. *Pediatrics* **113**: 73–76

Yeo TW, Roxburgh R, Maranian M *et al* 2003 Refining the analysis of a whole genome linkage disequilibrium association map: the United Kingdom. *J Neuroimmunol* **143**: 53–59

Yeo TW, Maranian M, Singlehurst S *et al* 2004 Four single nucleotide polymorphisms from the Vitamin D receptor gene in UK multiple sclerosis. *J Neurol* **251**: 753–754

Yiannoutsos CT, Major EO, Curfman B *et al* 1999 Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leucoencephalopathy. *Ann Neurol* **45**: 816–821

Yong VW 2002 Differential mechanisms of action of interferon-beta and glatiramer aetate in MS. *Neurology* **59**: 802–808

Yoshida EM, Rasmussen SL, Steinbrecher UP *et al* 2001 Fulminant liver failure during interferon beta treatment of multiple sclerosis. *Neurology* **56**: 1416

Yoshida T, Tanaka M, Sotomatsu A, Okamoto K 1999 Effect of methylprednisolone-pulse therapy on superoxide production of neutrophils. *Neurol Res* **21**: 509–512

Youl BD, Kermode AG, Thompson AJ *et al* 1991a Destructive lesions in demyelinating disease. *J Neurol Neurosurg Psychiatry* **54**: 288–292

Youl BD, Turano G, Miller DH *et al* 1991b The pathophysiology of acute optic neuritis: an association of gadolinium leakage with clinical and electrophysiological deficits. *Brain* **114**: 2437–2450

Younes-Mhenni S, Janier MF, Cinotti L *et al* 2004 FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes. *Brain* **127**: 2331–2338

Young AC, Saunders J, Ponsford JR 1976 Mental change as an early feature of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **39**: 1008–1013

Young IR, Hall AS, Pallis CA *et al* 1981 Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet* **ii**: 1063–1066

Young RB 1976 Fluorescein angiography and retinal venous sheathing in multiple sclerosis. *Can J Ophthalmol* **11**: 31–36

Young RR, Delwade PJ 1981a Drug therapy: spasticity (part 1). *N Engl J Med* **304**: 28–33

Young RR, Delwade PJ 1981b Drug therapy: spasticity (part 2). *N Engl J Med* **304**: 96–99

Young W, Rosenbluth J, Wojak JC *et al* 1989 Extracellular potassium activity and axonal conduction in spinal cord of the myelin-deficient mutant rat. *Exp Neurol* **106**: 41–51

Younger DS, Pedley TA, Thorpy MJ 1991 Multiple sclerosis and narcolepsy: possible similar genetic susceptibility. *Neurology* **41**: 447–448

Youssef S, Wildbaum G, Maor G *et al* 1998 Long-lasting protective immunity to experimental autoimmune encephalomyelitis following vaccination with naked DNA encoding C-C chemokines. *J Immunol* **161:** 3870–3879

Youssef S, Stuve O, Patarroyo JC *et al* 2002 The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature* **420**: 78–84

Yu JS, Hayashi T, Seboun E *et al* 1991 Fos RNA accumulation in multiple sclerosis white matter tissue. *J Neurol Sci* **103**: 209–215

Yu JS, Pandey JP, Massacesi L *et al* 1993 Segregation of immunoglobulin heavy chain constant region genes in multiple sclerosis sibling pairs. *J Neuroimmunol* **42**: 113–116

Yu WP, Collarini EJ, Pringle NP, Richardson WD 1994 Embryonic expression of myelin genes: evidence for a focal source of oligodendrocyte precursors in the ventricular zone of the neural tube. *Neuron* **12**: 1353–1362

Yu YL, Woo E, Hawkins BR *et al* 1989 Multiple sclerosis among Chinese in Hong Kong. *Brain* **112**: 1445–1467

Yuan J, Yankner B 2000 Apoptosis in the nervous system. *Nature* **407**: 802–809

Yudkin PL, Ellison GW, Ghezzi A *et al* 1991 Overview of azathioprine treatment in multiple sclerosis. *Lancet* **338**: 1051–1055

Yung SY, Gokhan S, Jurcsak J *et al* 2002 Differential modulation of BMP signaling promotes the elaboration of cerebral cortical GABAergic neurons or oligodendrocytes from a common sonic hedgehog-responsive ventral forebrain progenitor species. *Proc Natl Acad Sci USA* **99**: 16273–16278

Yushchenko M, Mader M, Elitok E *et al* 2003 Interferon-beta-1b decreased matrix metalloproteinase-9 serum levels in primary progressive multiple sclerosis. *J Neurol* **250**: 1224–1228

Zaffaroni M, Ghezzi A 2000 The prognosis value of age, gender, pregnancy and endocrine factors in multiple sclerosis. *Neurol Sci* **21 (Suppl)**: 857–860

Zajicek JP 1990 Sarcoidosis of the cauda equina: a report of three cases. *J Neurol* **237**: 244–246

Zajicek JP, Compston DAS 1994 Myelination *in vitro* of dorsal root ganglia by glial progenitor cells. *Brain* **117**: 1333–1350

Zajicek JP, Compston DAS 1995 Human oligodendrocytes are not sensitive to complement – a study of CD59 expression in the human central nervous system. *Lab Invest* **73**: 128–138

Zajicek JP, Wing M, Scolding NJ, Compston DAS 1992 Interactions between oligodendrocytes and microglia, a major role for complement and tumour necrosis factor in oligodendrocyte adherence and killing. *Brain* **115**: 1611–1631

Zajicek JP, Scolding NJ, Foster O *et al* 1999 Central nervous system sarcoidosis – diagnosis and management based on a large series. *Q J Med* **92**: 103–117

Zajicek JP, Fox P, Sanders H *et al* 2003 Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* **362**: 1517–1526

Zakrzewska-Pniewska B, Styczynska M, Podlecka A *et al* 2004 Association of apolipoprotein E and myeloperoxidase genotypes to clinical course of familial and sporadic multiple sclerosis. *Mult Scler* **10**: 266–271

Zamvil SS, Steinman L 1990 The T lymphocyte in experimental allergic encephalomyelitis. *Ann Rev Immunol* **8**: 579–622

Zamvil SS, Steinman L 2003 Diverse targets for intervention during inflammatory and neurodegenerative phases of multiple sclerosis. *Neuron* **38**: 685–688

Zamvil SS, Nelson PA, Trotter J *et al* 1985 T-cell clones specific for myelin basic protein induce chronic relapsing paralysis and demyelination. *Nature* **317**: 355–358

Zander H, Kuntz B, Scholz S, Albert ED 1976 Analysis for joint segregation of HLA and multiple sclerosis in families (abstract). In: Dausset J (ed.) *HLA and Disease*. Paris

Zander H, Abb J, Kaudewitz O, Riethmuller G 1982 Natural killing activity and interferon production in multiple sclerosis. *Lancet* **i**: 280

Zandman-Goddard G, Levy Y, Weiss P *et al* 2003 Transverse myelitis associated with chronic hepatitis C. *Clin Exp Rheumatol* **21**: 111–113

Zang YC, Samanta AK, Halder JB *et al* 2000a Aberrant T cell migration toward RANTES and MIP-1 alpha in patients with multiple sclerosis: overexpression of chemokine receptor CCR5. *Brain* **123**: 1874–1882

Zang YC, Yang D, Hong J *et al* 2000b Immunoregulation and blocking antibodies induced by interferon beta treatment in MS. *Neurology* **55**: 397–404

Zang YC, Halder JB, Samanta AK *et al* 2001 Regulation of chemokine receptor CCR5 and production of RANTES and MIP-1alpha by interferon-beta. *J Neuroimmunol* **112**: 174–180

Zang YC, Hong J, Robinson R *et al* 2003a Immune regulatory properties and interactions of copolymer-I and beta-interferon 1a in multiple sclerosis. *J Neuroimmunol* **137**: 144–153

Zang YC, Hong J, Rivera VM *et al* 2003b Human anti-idiotypic T cells induced by TCR peptides corresponding to a common CDR3 sequence motif in myelin basic protein-reactive T cells. *Int Immunol* **15**: 1073–1080

Zarei M, Chandran S, Compston A, Hodges J 2003 Cognitive presentation of multiple sclerosis: evidence for a cortical variant. *J Neurol Neurosurg Psychiatry* **74**: 872–877

Zayas MD, Lucas M, Solano F *et al* 2001 Association of a CA repeat polymorphism upstream of the Fas ligand gene with multiple sclerosis. *J Neuroimmunol* **116**: 238–241

Zee DS, Leigh JR 2002 Oculomotor control: normal and abnormal. In: Asbury AK, McKhann GM, McDonald WI *et al* (eds) *Diseases of the Nervous System: Clinical Neuroscience and Therapeutic Principles*. Vol 1. pp. 634–657

Zeine R, Owens T 1992 Direct demonstration of the infiltration of murine central nervous system by Pgp-1/CD44^{high}CD45RB^{low}CD4^{+} T cells that induce experimental allergic encephalomyelitis. *J Neuroimmunol* **40**: 57–70

Zeine R, Cammer W, Barbarese E *et al* 2001 Structural dynamics of oligodendrocyte lysis by perforin in culture: relevance to multiple sclerosis. *J Neurosci* **64**: 380–391

Zelenika D, Grima B, Pessac B 1993 A new family of transcripts of the myelin basic protein gene: expression in brain and in immune system. *J Neurochem* **60**: 1574–1577

Zeman AZJ, Kidd D, McLean BN *et al* 1996 A study of oligoclonal band negative multiple sclerosis. *J Neurol Neurosurg Psychiatry* **60**: 27–30

Zenker W, Bankoul S, Braun JS 1994 Morphological indications for considerable diffuse reabsorption of cerebrospinal fluid in spinal meninges particularly in the areas of meningeal funnels: an electron-microscopical study including tracing experiments in rats. *Anat Embryol* **189**: 243–258

Zenzola A, De Mari M, De Blasi R *et al* 2001 Paroxysmal dystonia with thalamic lesion in multiple sclerosis. *Neurol Sci* **22**: 391–394

Zettl UK, Gold R, Hartung H-P, Toyka KV 1994 Apoptotic death of T-lymphocytes in experimental autoimmune neuritis of the Lewis rat. *Neurosci Lett* **176**: 75–79

Zettl UK, Gold R, Toyka KV, Hartung H-P 1995 Intravenous glucocorticosteroid treatment augments apoptosis of inflammatory T cells in experimental autoimmune neuritis (EAN) of the Lewis rat. *J Neuropathol Exp Neurol* **54**: 540–547

Zettl UK, Mix E, Zielasek J *et al* 1997 Apoptosis of myelin-reactive T cells induced by reactive oxygen and nitrogen intermediates in vitro. *Cell Immunol* **178**: 1–8

Zhang J, Medaer R, Hashim GA *et al* 1992 Myelin basic protein-specific T lymphocytes in multiple sclerosis: precursor frequency, fine specificity, and cytotoxicity. *Ann Neurol* **32**: 330–338

Zhang J, Medaer R, Stinsson P *et al* 1993 MHC-restricted depletion of human myelin basic protein-reactive T cells by T cell vaccination. *Science* **261**: 1451–1454

Zhang J, Markovic-Plese S, Lacet B *et al* 1994 Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *J Exp Med* **179**: 973–984

Zhang J, Vandevyver C, Stinissen P, Raus J 1995 *In vivo* clonotypic regulation in human myelin basic protein-reactive T cells by T cell vaccination. *J Immunol* **155**: 5865–5877

Zhang J, Hutton G, Zang Y 2002 A comparison of the mechanisms of action of interferon beta and glatiramer acetate in the treatment of multiple sclerosis. *Clin Ther* **24**: 1998–2021

Zhang X, Izikson L, Liu L, Weiner HL 2001 Activation of CD25^{+}CD4^{+} regulatory T cells by oral antigen administration. *J Immunol* **167**: 4245–4253

Zhang X-M, Heber-Katz E 1992 T cell receptor sequences from encephalitogenic T cells in adult Lewis rats suggest an early ontogenic origin. *J Immunol* **148**: 746–752

Zhang X, Cai J, Klueber KM *et al* 2005 Induction of oligodendrocyte from adult human olfactory epithelial-derived progenitors by transcription factors. *Stem Cells* **23**: 442–453

Zhang Z, Duvefelt K, Svensson F *et al* 2005 Two genes encoding immune-regulatory molecules (LAG3 and IL7R) confer susceptibility to multiple sclerosis. *Genes Immun* **6**: 145–152

Zhou L, Messing A, Chiu SY 1999 Determinants of excitability at transition zones in Kv1.1-deficient myelinated nerves. *J Neurosci* **19**: 5768–5781

Zhou Q, Anderson DJ 2002 The bHLH transcription factors OLIG2 and OLIG1 couple neuronal and glial subtype specification. *Cell* **109**: 61–73

Zhou Q, Wang S, Anderson DJ 2000 Identification of a novel family of oligodendrocyte lineage-specific basic helix-loop-helix transcription factors. *Neuron* **25**: 331–343

Zhou Q, Rammohan K, Lin S *et al* 2003 CD24 is a genetic modifier for risk and progression of multiple sclerosis. *Proc Natl Acad Sci USA* **100**: 15041–15046

Ziemssen T, Kumpfel T, Klinkert WEF *et al* 2002 Glatiramer acetate-specific T-helper 1- and 2-type cell lines produce BDNF: implications for multiple sclerosis therapy. *Brain* **125**: 2381–2391

Zihl J, Werth R 1984 Contributions to the study of 'blind sight'. II The role of specific practice for saccadic localisation in patients with postgeniculate visual field defects. *Neuropsychologia* **22**: 13–22

Zipp F, Weber F, Huber S *et al* 1995 Genetic control of multiple sclerosis: increased production of lymphotoxin and TNFα by HLA-DR2+ T cells. *Ann Neurol* **38**: 723–730

Zipp F, Kerschensteiner M, Dornmair K *et al* 1998 Complexity of the anti-T cell receptor immune response: implications for T cell vaccination therapy of multiple sclerosis. *Brain* **121**: 1395–1407

Zipp F, Weil JG, Einhaupl KM 1999 No increase in demyelinating disease after hepatitis B vaccination. *Nature Med* **5**: 964–965

Zipp F, Windemuth C, Pankow H *et al* 2000a Multiple sclerosis associated aminoacids of polymorphic regions relevant for the HLA antigen binding are confined to HLA-DR'. *Hum Immunol* **61**: 1021–1030

Zipp F, Wendling U, Beyer M *et al* 2000b Dual effect of glucocorticoids on apoptosis of human autoreactive and foreign antigen-specific T cells. *J Neuroimmunol* **110**: 214–222

Zivadinov R, Rudick RA, De Masi R *et al* 2001a Effects of IV methylprednisolone on brain atrophy in relapsing–remitting MS. *Neurology* **57**: 1239–1247

Zivadinov R, Sepcic J, Nasuelli D *et al* 2001b A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing–remitting multiple sclerosis. *J Neurol Neurosurg Psychiatry* **70**: 773–780

Zivadinov R, Uxa L, Zacchi T *et al* 2003a HLA genotypes and disease severity assessed by magnetic resonance imaging findings in patients with multiple sclerosis. *J Neurol* **250**: 1099–1106

Zivadinov R, Iona L, Monti-Bragadin L *et al* 2003b The use of standardized incidence and prevalence rates in epidemiological studies on multiple sclerosis: a meta-analysis study. *Neuroepidemiology* **22**: 65–74

Zivadinov R, Zorzon M, Locatelli L *et al* 2003c Sexual dysfunction in multiple sclerosis: a MRI, neurophysiological and urodynamic study. *J Neurol Sci* **210**: 73–76

Zorgdrager A, De Keyser J 1998 Premenstrual exacerbations of multiple sclerosis. *J Neurol Neurosurg Psychiatry* **65**: 279–280

Zorzon M, Zivadinov R, Bosco A *et al* 1999 Sexual dysfunction in multiple sclerosis: a case-control study. 1. Frequency and comparison of groups. *Mult Scler* **5**: 418–427

Zorzon M, Ukmar M, Bragadin LM *et al* 2000 Olfactory dysfunction and extent of white matter abnormalities in multiple sclerosis: a clinical and MR study. *Mult Scler* **6**: 386–390

Zorzon M, Zivadinov R, Bragadin LM *et al* 2001 Sexual dysfunction in multiple sclerosis: a 2-year follow up study. *J Neurol Sci* **187**: 1–5

Zorzon M, Zivadinov R, Locatelli L *et al* 2003a Correlation of sexual dysfunction and brain magnetic resonance imaging in multiple sclerosis. *Mult Scler* **9**: 108–110

Zorzon M, Zivadinov R, Nasuelli D *et al* 2003b Risk factors of multiple sclerosis: a case-control study. *Neurol Sci* **24**: 242–247

Zorzon M, Zivadinov R, Locatelli L *et al* 2005 Long-term effects of intravenous high dose methylprednisolone pulses on bone mineral density in patients with multiple sclerosis. *Eur J Neurol* **12**: 550–556

Zouali H, Faure-Delanef L, Lucotte G 1999 Chromosome 19 locus apolipoprotein C-II association with multiple sclerosis. *Mult Scler* **5**: 134–136

Zoukos Y, Kidd D, Woodroofe MN *et al* 1994 Increased expression of high affinity IL-R receptors and β-adrenoceptors on peripheral blood mononuclear cells is associated with clinical and MRI activity in MS. *Brain* **117**: 307–315

Zsombok A, Schrofner S, Hermann A, Kerschbaum HH 2000 Nitric oxide increases excitability by depressing a calcium activated potassium current in snail neurons. *Neurosci Lett* **295**: 85–88

Zucchi I, Bini L, Valaperta R *et al* 2001 Proteomic dissection of dome formation in a mammary cell line: role of tropomyosin-5b and maspin. *Proc Natl Acad Sci USA* **98**: 5608–5613

Zwemmer JNP, van Veen T, van Winsen L *et al* 2004 No major association of ApoE genotype with disease characteristics and MRI findings in multiple sclerosis. *Mult Scler* **10**: 272–277