Experimental models of multiple sclerosis
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Purpose of review
Multiple sclerosis (MS) is a disease of the central nervous system of unknown cause. There are many medications available for the disease, but none are clearly effective in ameliorating its long-term disabling effects. MS is felt to be most likely either due to an aberrant immune response or a pathogen, or possibly a combination of the two, and the animal models available reflect these two possible pathogeneses. The hallmarks of the disease are demyelination, inflammation, axonal injury, and progressive disability. This review explores the experimental models of multiple sclerosis.

Recent findings
There are a variety of forms of experimental allergic encephalomyelitis, the most commonly studied animal model of MS. Two viruses, Theiler's murine encephalomyelitis virus and murine hepatitis virus, are used to induce infectious models of the disease.

Summary
The animal models have their advantages and disadvantages, but no model fully reproduces the spectrum of the human disease.

Keywords
animal models, autoimmunity, demyelination, multiple sclerosis, virus

Introduction: the utility of animal models
Multiple sclerosis (MS) is a uniquely human disease. It does not occur naturally in any other animal. Similarly, no animal models of MS mimic all of the features of the human disease faithfully. However, animal models of MS are important because they allow us to learn about the different aspects of disease, particularly neuroinflammation, and its link to demyelination, neuronal injury, and disability. The two main types of models – autoimmune and viral – also teach us about how the central nervous system (CNS) participates in the inflammatory process and how damage can occur during neuroinflammation caused by different stimuli. We learn something from each model, and it is important to assess information obtained from each one as contributing to our knowledge base, rather than having direct translation to the human disease. This point is frequently lost on individuals who wish to rush preliminary information about models directly to MS treatments. This eagerness is understandable in MS patients, who are desperate for more effective therapies. But clinicians and scientists must take the long view, and place new information in context of the strengths and weaknesses of each model.

Trying to faithfully model MS is frustrating. First, the etiopathogenesis is unknown. The two main types of models, autoimmunity and virus, are based on reasonable hypotheses, but there is no strong evidence that MS is due to either an autoimmune or a viral process and, in fact, the underlying cause may not be the same in all patients. Second, MS is multifaceted, involving attacks, progressive disability, axonal damage, compensatory axonal processes, demyelination, remyelination, inflammation, suppression of inflammation, and excessive immunoglobulin production within the CNS. Specific models can focus on only a few of these aspects of MS at a time, and none reproduces the whole spectrum of the disease. Third, the ideal use of an animal model is to provide information about basic biological processes within the CNS with some relevance to MS, but increasingly there is pressure from patients and funding agencies to translate work in animal models to human disease too rapidly. Despite these and other problems, the use of animal models for MS has continued to be used extensively, and indeed provides the most common research focus within neuroimmunology.

Not discussed here will be the toxin-induced models of demyelination such as those induced by cuprizone, lysolecithin, and ethidium bromide, which are reviewed elsewhere [1,2]. These models are helpful to understand demyelination and remyelination, but do not reproduce other aspects of MS, such as inflammation and axonal loss.

Autoimmune models: experimental allergic encephalomyelitis
Under certain conditions provoking an autoimmune response in the CNS, animals can develop inflammation,
As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral. As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral. As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral. As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral. As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral. As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral. As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral. As no animal model is completely faithful to the human disease, extrapolations of information gained from the much-needed information about inflammation, demyelination, and injury in the central nervous system. There are two main forms of multiple sclerosis models: autoimmune and viral.
large percentage of T cells. These mice develop EAE simply with the administration of pertussis toxin. Another way of producing EAE in an animal is transfer of cell populations or immunoglobulin [14] into naive mice, which allows the determination of which types of cells or antibody are important for EAE induction. Another interesting recently developed model is that of focal lesions causing demyelination, inflammation, and weakness, induced by intraspinal injection of the protein vascular endothelial growth factor (VEGF) in rats with high levels of anti-MOG antibodies [15]. These variations of the ‘standard’ EAE provide greater opportunities to learn about the biology of EAE.

Time course

The natural course of most forms of EAE is the development of weakness within about a week after immunization, with disability peaking at about 10–14 days after immunization, followed by resolution to baseline strength by 3–4 weeks after immunization. The demyelination and inflammation in the CNS usually follows this temporal pattern also. The weakness in EAE is usually associated with flaccidity, that is, decreased muscle tone. The flaccidity found in EAE may be because of the fact that many EAE models have nerve or nerve root involvement. Most EAE investigators use a relatively subjective visual assessment grading scale of zero to five plus for grading weakness rather than objective neurobehavioral analyses. There are many variations on this model, as mutant mice (see above) can be genetically engineered to overexpress or underexpress a wide variety of genes that have effects on the course of EAE.

The chronology of EAE mimics that of postvaccinal autoimmune encephalomyelitis. Stage 1 is the immunization with the encephalitogen. In contrast to postvaccinal encephalomyelitis, in which the main reason for the immunization is protection from rabies, and the sensitization to CNS antigens is an unwanted side-effect, in EAE, the sensitization to the encephalitogen is the main purpose of the immunization. In stage 2, usually in the first few days after the immunization, local lymph nodes drain the site of immunization, and the antigen is processed within these nodes by dendritic cells and other antigen-processing cells such as macrophages. By the end of the first week, in stage 3, CNS antigen-specific lymphocytes proliferate and enter the circulation, and begin to enter the CNS. Their entry into the CNS at this stage requires their passage through the blood–brain barrier, an event that has been extensively investigated [16]. Once they enter the CNS, they are retained there, presumably by the local presence of the antigen, and do not traffic out of the CNS; most lymphocytes with specificities for other antigens are not retained in the CNS, and either traffic back into the circulation, or alternatively apoptosis within the CNS, that is, undergo programmed cell death (PCD).

Stage 4, spanning from about day 10 to 20 after immunization, represents the period of most active inflammation within the CNS, and also is the period of the development of maximum neurological signs in the animal. The animal’s spinal cord, normally containing only an occasional mononuclear cell, will have sites of large numbers of them, mostly lymphocytes and macrophages. Initially, mononuclear cells accumulate in the perivascular space between the basement membranes of the cerebrovascular endothelial cells and of the basement membrane associated with astrocytic endfeet. Over time, the mononuclear cells move through the basement membrane and the glia limitans comprised of astrocytic endfeet, and into the parenchyma of the CNS. Demyelination also appears at this stage, although the extent of demyelination varies widely in different models of EAE.

By 3 weeks after immunization in stage 5, inflammation is abating and recovery is beginning. EAE in most models is monophasic and after the peak of inflammation and disease, animals improve relatively rapidly, often to being completely normal. In some EAE models, there is fixed injury to the CNS and the animals improve after the peak of disease, but do not completely recover back to their baseline.

Some EAE models are described as being ‘chronic’ or ‘relapsing’ [17]. However, the degree of chronicity is usually mild. For instance, in a recent publication authors evaluated a therapy, surgical lymph node excision, in three different models of mouse EAE, which they described as ‘acute, chronic, and chronic relapsing’, induced by immunizing SJL, C57Bl/6, or Biozzi ABH mice with proteolipid protein peptide, myelin oligodendrocyte glycoprotein peptide (35–55), or myelin oligodendrocyte glycoprotein (8–21) [18]. However, although there were minor differences in the course of the neurological disability in these mice, in all three groups of animals the disability peaked at 10–15 days after immunization and had completely resolved by the end of the second month. Thus, EAE is generally a monophasic phenomenon, and, given the absence of accumulating neurological injury, it is not a good model for the progressive disability of MS.

Models of neuromyelitis optica

Neuromyelitis optica (NMO), a cousin of MS, is an important disease for at least three reasons: first, it is frequently a particularly devastating illness causing progressive visual loss and spinal cord injury; second, it is frequently misdiagnosed as MS and needs to be differentiated from that disease because treatment is different [19]; and third, its etiopathogenesis is much better defined than MS in that it appears to be caused by an autoantibody [20]. For all these reasons, there has been an extensive interest in developing animal models, and a
number of laboratories have been successful [21,22*]. In these models, the mediator of injury is IgG from patients with NMO which results in injury either after being directly injected into the CNS or via intravenous injection after inducing EAE and opening the blood–brain barrier. The pathogenic IgG can be either isolated directly from the blood of NMO patients or can be made by recombinant technology. Thus, these models fall into a category of experimental models called passive transfer in which the disease can be induced in a normal animal by injection of pathogenic immunoglobulin or cells.

What autoimmune models have taught us about the biology of central nervous system neuroinflammation

EAE models have been utilized extensively by investigators interested in basic immunobiology, and have been considered examples of archetypal T-cell-mediated inflammatory disease. The models have taught us a great deal about how pathogenic T cells are activated and how they might interact with cells within the CNS. T cells are in the lymphocyte class of white blood cells, and have on their surface the CD3 molecule; the name comes from the fact that they passage through the thymus early in their development. T cells that traffic to the CNS are considered part of the ‘adaptive’ immune response because they can molecularly ‘adapt’ antigen receptors to deal with the particular antigen of the moment. Ground-breaking work by Ben-Nun et al. [23] in the early 1980s revealed that T cells could mediate EAE, which led to hope that a new era of understanding EAE and possibly MS was dawning. Since then, the T cell has been the primary cell type studied in EAE.

T cells must be activated to enter the CNS and promote EAE, and the mechanisms by which antigen-specific T cells are activated and subsequently enter the CNS have been a major focus of EAE research. An increased understanding of the ‘trimolecular complex’ of MHC molecule–antigen–T-cell receptor has come partly through a great deal of study of these molecules in EAE research. The classical inflammatory T cell studied has been the CD4+ Th1 cell which requires MHC class II-positive antigen-presenting cells, and releases interferon-gamma, interleukin (IL)-12, and tumor necrosis factor-alpha (TNFalpha), although other T-cell types are likely important also.

The mechanisms by which lymphocytes traffic through the body, and especially of how activated T cells enter the CNS has also benefitted from studies in EAE models. In the mid-1980s, immunologists investigated how immune responses were regulated by controlling the access of white cells to sites of inflammatory sites, and found that white cells use a variety of receptors to recognize specific vascular ligands or ‘addressins’ associated with specific blood vessels. This class of molecules, sometimes called adhesion molecules, also were found to be important in many cell-to-cell interactions through the body. Blocking these molecules in therapy of inflammatory disease was considered possible for a long list of inflammatory diseases very soon after their discovery, and in the early 1990s a number of laboratories demonstrated the importance of these molecules in EAE by showing that blocking adhesion molecules resulted in substantial improvement in the course of EAE in the rat [24] and in mice [25].

More recently, EAE has been used to study the role of B cells in the CNS. B cells, a class of lymphocytes that express CD19 and CD20 on their surface and are part of the adaptive immune response, have not been a major focus of EAE researchers until the recent demonstration that B-cell depletion using the anti-CD20 monoclonal rituximab was successful in decreasing inflammatory activity in MS [26,27]. In the past, they had been simply thought of being possibly important in pathogenesis by producing autoantibodies in MS [28]. However, the positive effects of rituximab in MS occurred without affecting the production of antibodies within the CNS [29], indicating that the effect of B-cell depletion was likely because of either a loss of antigen presentation by B cells or a B-cell-specific cytokine. Studies in EAE using B-cell depletion have thus far demonstrated variable results depending on when B-cell depletion was performed, that is, treatment with B-cell depletion prior to encephalitogen exposure exacerbated MOG-induced EAE, whereas later treatment ameliorated the course [30,31*]. The data, from studies in both rodents and humans, indicate that the B-cell compartment is more complex than once thought, and may be an important contributor both to disease improvement or exacerbation.

Experimental allergic encephalomyelitis models and injury to the central nervous system

Less is known about the effector mechanisms, once the activated cells enter the CNS. The precise type of T cell or mixture of T cells that are most pathogenic in EAE is still a matter of controversy. In Ben-Nun’s original manuscript describing T-cell mediation of EAE [23], lymphocyte lines were utilized. These were complex mixtures of T cells, not T-cell clones, and since that pivotal observation, populations of T cells, presumably interacting together, rather than a monoclonal population, have been the most potent effectors. Most investigators until recently assumed that the most pathogenic cells were CD4+, interferon-gamma secreting cells (sometimes called Th1 cells). Recently, other T cells that can induce EAE such as Th2 cells, Th17 cells, and CD8+ cells have also been studied, leading to the conclusion that a variety of T cells may participate in neuroinflammation. Of the above T-cell types, the most interest has focused on the Th17 cell [32], CD4+ T cells that secrete IL-17, which
are developmentally distinct from Th1 and Th2 cells. In humans, these cells are induced by a combination of IL-23, IL-1beta, and TGFbeta, and secrete IL-22 as well as IL-17. It appears that the injury to the CNS in most forms of EAE is caused by a complex mixture of components that cannot be reproduced by a single cell type. The requirements for maximal disease in any system are variable. For instance, anti-MOG antibody is necessary for maximum clinical disease in some models of MOG-induced EAE, and weakness can be amplified by the administration of anti-MOG monoclonal antibodies, but not antibodies to irrelevant antigens, whereas other forms of MOG-induced EAE, such as those induced when MOG peptides are used as encephalitogens in C57Bl/6 mice, can be induced by T cells alone.

Many investigators believe that the pathogenicity of T cells in the CNS derives from their release of cytokines, which may be toxic to CNS cells. One of the leading candidates for this ‘toxic’ cytokine is TNFalpha [33], a cytokine known to have potent proinflammatory actions. Blockade of TNFalpha ameliorated the disease in EAE models [34,35]. Another critical cytokine for CNS inflammation in EAE has been IL-23, which appears to be essential for Th17 polarization and pathogenicity [36], although the precise mechanism by which IL-23 contributes to CNS inflammation and injury is unknown. A third cytokine thought important in pathogenesis was B cell activation factor of the TNF family (BAFF) [37]. It is interesting that efforts to target these cytokines in human disease have led to worsening or, at best, no effect in MS.

**Viral models**

CNS demyelination is produced by a wide variety of viruses in animals [38]. The list of naturally occurring viral demyelinating models includes visna virus infection in Icelandic sheep, caprine arthritis-encephalitis virus infection in goats, Semliki Forest virus in mice, and canine distemper and its variants in dogs and sea mammals. These viruses represent a broad spectrum of viruses without any similarities, except that they all are RNA viruses. The most widely used viral models for MS are the Theiler’s murine encephalomyelitis virus (TMEV) and murine hepatitis virus (MHV) models.

TMEV is a picorna virus, a very small virus of only 8100 nucleotides in the Cardiovirus genus. After intracerebral injection of the virus into a mouse, there are two phases of the disease. The first is an acute, mild, usually subclinical encephalitis, but if too much virus is injected or if the mouse is immunosuppressed the encephalitis can be deadly [39]. During this first phase, the infection is predominantly of neurons. The chronic phase, sometimes called TMEV-induced demyelinating disease (TIDD), beginning about a month after infection, consists of slowly progressive disability, characterized by demyelination, remyelination [1], inflammation, and axonal damage [40]. The weakness is associated with spasticity and occasionally severe muscle spasms. The viral load in the CNS in the chronic phase is stable over time, with viral replication [41] occurring concurrently with immune-mediated viral clearance, to a large extent mediated by high levels of antibody in the CNS [42,43] produced by resident plasma cells [44,45].

The primary reservoirs of chronic infection are microglia and macrophages, although oligodendrocytes and astrocytes are also infected [46]. The progressive damage to the CNS is presumed to be because of the large amount of inflammation, although, as in EAE, the actual effectors leading to demyelination and axonal injury are unknown. Except for the lack of relapses, the clinical picture resembles human MS; the disorder is very similar also, as is the presence of plasma cells and production of IgG within the CNS. A disadvantage for researchers, though, is that mice can take months to become weak after the initial infection; in contrast, weakness in EAE occurs within a few weeks of immunization.

In the MHV model, also called JHMV from the most commonly used strain of mouse hepatitis virus, demyelination, inflammation, and high viral levels in the CNS occur as a monophasic event, followed by slow diminution of viral load and partial resolution of demyelination and inflammation. However, the virus is not completely cleared and new areas of demyelination appear for prolonged periods, possibly because of local reactivation of virus in areas of the CNS [38]. The early encephalitis in MHV infection is also used as a model of acute viral encephalitis.

Canine distemper virus (CDV) and other related viruses are morbilliviruses related to measles virus that cause demyelination in a variety of animals in the wild; these viruses are the subjects of some recent reviews [47,48]. The most medically important morbillivirus is measles virus that generally causes an acute viral illness in children, and has a significant mortality especially in the developing world where measles vaccination is less common. Measles virus, however, also causes two rare syndromes called subacute sclerosing panencephalitis (SSPE) and measles inclusion body encephalitis (MIBE); SSPE can mimic MS. CDV, which in the wild has primarily affected dogs but also wild cats and other mammals, initially causes a systemic infection, transmitted through the lungs, that ultimately invades the CNS, and results in glial cell infection. Subsequently, the virus persists chronically and causes multifocal, inflammatory demyelinating lesions strongly resembling MS. The precise pathogenesis of the lesions is controversial, but appears to be related to a combination of persistent virus, macrophage activation, strongly
Inflammatory diseases and infection

upregulated cytokine responses, and an inflammatory disorder consisting of perivascular infiltration with plasma cells and lymphocytes. Oligodendrocytes, though infected by CDV, are not lysed. Morbilliviruses also cause inflammatory demyelination in marine mammals including seals, dolphins, whales, and porpoises.

Retrovirus infections can also cause demyelinating, inflammatory disease in animals; the most well known retrovirus causing human disease is human immunodeficiency virus (HIV). Visna virus was the first retrovirus isolated in 1957, and is similar to TMEV in causing a subacute encephalitis, followed by a chronic demyelinating encephalomyelitis; susceptible animals are sheep. Of note is the fact that visna virus causes sharply demarcated plaques in the brain and spinal cord, similar to the plaques in MS. Another retrovirus causing demyelination is caprine arthritis encephalitis virus (CAEV), which causes inflammatory demyelination in the brain and spinal cord in young goats.

The utility of animal models in preclinical testing for therapy of multiple sclerosis

EAE, the autoimmunity-based animal model, is not seen as inherently superior to (viral) models like Visna or TMEV ... One might be right to regard autoimmunity as a paradigm shift that never quite made it! Byron H. Waksman [49]

Is the underlying cause autoimmune or viral?

In order for a model to be highly predictive of the human disease, the pathogenesis of the model should be identical to, or at least very close, to the human disease. Thus, autoimmune or viral models may not be highly predictive if the cause of MS is neither because of autoimmunity nor a pathogen. The prevailing hypothesis for the cause of MS for the past 50 years has been autoimmunity, but MS has a long history of having ‘prevailing hypotheses’ which are later abandoned. A spiritual disorder, glial scarring, thromboemboli, degenerative myelin breakdown, and measles virus all appeared to be plausible as a cause of MS at the time they were espoused; none of them are now thought to be likely. There is little question that most attacks of MS have inflammatory features and medications known to downregulate the immune response decrease the likelihood of attacks. However, decreasing attacks is not the same as improving the natural history of the disease [50,51]. Attacks after the first few years of disease do not correlate with ultimate physical disability. On the basis of autoimmunity hypothesis, with EAE being the logical model, there has been a tendency to utilize increasingly aggressive immunosuppression in MS, and therapies such as cyclophosphamide, mitoxantrone, and natalizumab, which have substantial risks, have been utilized more and more. Without strong evidence in support of MS being autoimmune in nature [52], and with the inability of EAE to predict response to new therapies (see below), new non-EAE models, especially viral models, are being increasingly utilized.

There is no strong evidence that the cause of MS is a virus, either, but the TMEV model has a number of advantages over EAE models as outlined in below. The progressive disability of the TMEV model is particularly attractive as a target, as neurologists, at this time in the history of MS, have a plethora of therapies that have been shown to be effective for exacerbations, and what is needed are therapies that affect disability progression. In both MS and TMEV, both diseases progress through 20–25% of the lifespan of the animal and then usually plateau, that is, neither patients nor mice tend to die of progressive neurological disability. Both TMEV and MS have prominent involvement of the humoral arm of the immune response, with antibody being both produced and deposited in the CNS; in contrast, in most, but not all, models of EAE, there is little evidence of B-cell or antibody involvement. Neither TMEV nor EAE mirror the combination of exacerbations/remissions and progressive disability of the human disease.

For practicality of use, EAE is a much easier model to use. Peak weakness usually occurs in a week or two after immunization, whereas weakness in TIDD usually takes a few months to develop. The reagents needed to induce EAE (i.e. adjuvant, myelin peptides or proteins, and pertussis) can be bought, whereas live viruses need to be grown in tissue culture in TIDD, and their activity is not easily quantitated. Vivariums have no difficulty with EAE experiments, whereas many animal facilities refuse to deal with such mouse pathogens as TMEV or MHV.

Thus, at this point in time, as noted by Byron Waksman at the beginning of this section, neither model is ‘inherently superior’.

Can models predict the utility of multiple sclerosis therapies?

EAE models have historically been used preclinically to assess MS therapies. As discussed above, because of the many dissimilarities between the animal model and the human disease, a direct extrapolation of findings in EAE to MS is unwarranted. Blockade of three different cytokines thought to be important in inflammation in EAE, TNFalpha, BAFF, and IL-23, were found either to worsen MS [53,54] or to have no effect [55]. As one author states, ‘the failure of the clinical trial with Atacicept targeting BAFF and its relative APRIL, was a great surprise and cannot readily be explained’ [54]. Three recent reviews have warned about the dangers of a reliance on EAE to predict responses to therapies in
MS. Sriram and Steiner [56] concluded that EAE is a misleading model of MS, and made a reasonable argument that EAE has been inappropriately used to provide a framework for attempts to understand MS. Friese et al. [57] pointed out the poor track record of EAE in predicting response to therapies, and decried ‘our rudimentary understanding of the key pathogenetic mechanisms in EAE models’. Mix et al. [58] thought EAE to be more suitable for the studies of immunogenetics and histopathology rather than for screening of new treatments, and warned that ‘translation of experimental results into clinical practice requires prudence and great caution’.

Are the ‘Theiler’s model or other viral models better predictors? As attacks are not a feature of the viral models, and because current therapies are usually approved by the US Food and Drug Administration for effect on attacks, it is unlikely that companies testing therapies will use viral models to guide drug development in isolation. On the contrary, if amelioration of disability progression becomes a requirement for approval in the future, viral models will be much more likely to be more commonly utilized. Whether they will truly be predictive of effect on disability progression, only time will tell.

So, given the failures of EAE models, should EAE research be abandoned? No. EAE is important as a means to understand inflammation in the CNS. Despite its limitations, much will continue to be learned from EAE about a wide variety of phenomena relevant to human disease including the blood–brain barrier, effects of resident CNS populations, immune cell trafficking through the CNS, and cytokine production and cytokine effects.

Lessons from animal models of stroke

Investigators utilizing MS models can benefit from lessons learned in recent experience in animal models of stroke. Stroke is one of the most common injuries to the CNS, and current therapy for stroke, as for MS, is suboptimal. In stroke, as in MS, animal models are extensively used in order to learn more about the basic biology of the stroke process as well as to predict success of therapies. In 1999, a group of stroke investigators from academia and industry formed a group called Stroke Therapy Academic Industry Roundtable (STAIR) and met to provide recommendations for the preclinical development of acute ischemic stroke therapies. From 2000 to 2009, drugs which appeared to be successful in preclinical models failed to demonstrate efficacy in clinical trials. The STAIR met again in 2009 to address why there were so many failures of preclinical trials to identify successful candidates [59]. One conclusion was that there was considerable bias in the design of the studies resulting in overestimating the effectiveness of the intervention [60]. In addition, testing of only five of the 550 drugs reported to be effective in animal models of focal ischemia fully met with the original 1999 STAIR recommendations [61]. Investigators in stroke models recommended that standards in research for animal studies be adhered to in a similar manner to those for clinical trialists, that is, Consolidated Standards of Reporting Trials (CONSORT).

A similar academia–industry combined approach could be implemented in animal models of MS. It would be advantageous to all concerned to utilize the standards that would make the predictive value of preclinical testing as high as possible. A number of changes in current procedures, recommended by STAIR [59], would likely need to be implemented. First, opportunities for bias need to be minimized; in many studies of EAE models bias is likely, as the readout of clinical disease is usually highly subjective, and frequently the individual performing the analysis is aware of the treatment status of the groups. The opportunity for bias would be minimized by using objective measures of strength and coordination such as the Rotarod analysis [40,42], and ensuring that all evaluators are blinded. Second, findings in one laboratory should be reproduced in a separate, independent laboratory. Frequently, in studies in EAE models, findings are hard to reproduce, raising concerns about the reliability of the original observations. Third, careful histological assessment should be utilized to confirm data. Thus, if a laboratory identifies improvement in the course of disability progression in TIDD, ideally that would be confirmed by an associated improvement in axonal damage or demyelination. Fourth, verification in more than one animal model is ideal, and STAIR recommends moving to a cat or nonhuman primate model if work in a rodent model indicates efficacy. Finally, appropriate biomarkers should ideally be identified in the animal model so that they can also be utilized in human studies.

Conclusion

Models of MS have provided, and will continue to provide, much needed information about the link between inflammation, demyelination, axonal injury, and disability. However, direct extrapolation of data obtained in these models to the human disease is generally not justified, and the effect of therapeutic interventions in the models must be interpreted with care.
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