Commentary

Optic Neuritis, A New Variant of Experimental Encephalomyelitis, A Durable Model for All Seasons, Now In Its Seventieth Year

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One of the most enduring models of human disease now celebrates the seventieth anniversary of its publication in The Journal of Experimental Medicine. Thomas Rivers, working at the Hospital of the Rockefeller Institute for Medical Research, along with his colleagues D.H. Sprunt and G.P. Berry, submitted the article entitled, “Observations on Attempts to Produce Disseminated Encephalomyelitis in Monkeys,” on Feb. 21, 1933 (1). Rivers established this model to try to understand what caused neurological reactions to certain viral infections like smallpox and in some circumstances to vaccinations like rabies: the very first sentence of this landmark paper reads, “During convalescence from certain diseases notably smallpox, vaccinia and measles, and during or following vaccination against rabies, an occasional patient develops symptoms and signs referable to the central nervous system.” One of the most devastating complications of vaccination and viral infection is acute optic neuritis (2). In the current issue, Bettelli and colleagues have been able to establish a model of acute optic neuritis, without accompanying inflammation elsewhere in the central nervous system (3).

The Optic Neuritis Model of EAE. There are multiple forms of autoimmune demyelination. About 10 to 30% of patients with multiple sclerosis have a clinical presentation that starts with an attack of optic neuritis, sometimes accompanied by other findings (4). Rates vary due to ascertainment biases: ophthalmologists may report higher rates than neurologists, for the obvious reason that patients and referring physicians turn to ophthalmologists first. In some cases there is optic neuritis without obvious evidence of inflammation outside the visual system. About a third of the time optic neuritis is a harbinger of further attacks elsewhere in the central nervous system leading to a diagnosis of multiple sclerosis. To date there have been no reproducible experimental systems where we have a model of either pure optic neuritis, optic neuritis plus inflammation elsewhere in the central nervous system, or inflammation elsewhere in the central nervous system without optic neuritis. In this issue, Bettelli and colleagues have discovered such models in a transgenic mouse with TCRs recognizing the major encephalitogenic epitope of myelin oligodendroglial glycoprotein (MOG) in H-2b mice (3). 30% of these MOG-specific TCR transgenic mice spontaneously develop pure optic neuritis. The optic nerve interestingly contains more MOG, than elsewhere in the central nervous system. If these transgenic mice are immunized with MOG35–55 plus pertussis toxin, then they develop optic neuritis plus inflammation elsewhere in the central nervous system. The role of an exogenous toxin in this model of genetically determined autoimmunity, provides a brilliant opportunity to assess the interplay of genes and environment in autoimmunity.

The Topology of Immunology: Autoimmunity and Allergy Are Joined In EAE. Since its first description by Rivers the model has served as a starting point for our understanding of autoimmunity (Table I). The “A” in the acronym EAE, mutated from experimental allergic to experimental autoimmune encephalomyelitis, sometime in the 70’s (Table II). Now the boundaries between these two seemingly opposite poles of immunity are coming together as if the contour of immunity was more spherical than flat. We are learning from studies on the EAE model that components of the allergic response are critical in the modulation of Th1 autoimmunity (5, 6).

The boundary between allergy and autoimmunity can be blurred: it is possible to induce “horror autotoxicus” with anaphylaxis against certain self-antigens, exemplified by myelin peptides (5). Further, Th2 T cells are capable of inducing EAE with features that include eosinophilic inflammation, sometimes also present in MS (7). Furthermore mast cells are present in MS lesions, and PAF-R and tryptase are elevated in the spinal fluid of MS patients (6, 8). Analysis of mRNA from multiple sclerosis (MS) lesions revealed increased amounts of transcripts for several genes encoding molecules traditionally associated with allergic responses, including prostaglandin D synthase (PGDS), histamine receptor type 1 (H1R), platelet acti-
autoimmunity are not antipodal. Both Th1 responses and "allergic" responses: allergy and elimination must now be viewed as encompassing elements of metrically opposite to allergy. The pathogenesis of demyelination must now be viewed as encompassing elements of the immune system. CRF can down-regulate Th1 responses associated with allergy in autoimmune demyelination. Histamine receptor genes confer susceptibility to EAE (10). Th1 cells reactive to proteolipid protein (PLP) expressed more H1R and less H2R than Th2 cells. An H1R antagonist, blocked EAE and a PAFR antagonist reduced the severity of EAE. EAE severity was also decreased in mice with disruption of the genes encoding Ig Fc receptor 1 (FcεRI), and tryptase (8, 9).

In EAE, mediated by Th1 T cells, histamine receptor 1 and 2 (H2R) are present on inflammatory cells in brain lesions. Histamine receptor genes confer susceptibility to EAE (10). Th1 cells reactive to proteolipid protein (PLP) expressed more H1R and less H2R than Th2 cells. An H1R antagonist, blocked EAE and a PAFR antagonist reduced the severity of EAE. EAE severity was also decreased in mice with disruption of the genes encoding Ig FcγRIII and both FcεRI and FcεRI. PGDS and tryptase transcripts were elevated in EAE brain (6). EAE is attenuated in mast cell–deficient mice (11). Taken together, these data reveal extensive involvement of elements of the immune response associated with allergy in autoimmune demyelination. The role of mast cells in autoimmune disease also presents a challenge to our understanding of the pathophysiology of these disorders, previously thought to be diametrically opposite to allergy. The pathogenesis of demyelination must now be viewed as encompassing elements of both Th1 responses and "allergic" responses: allergy and autoimmunity are not antipodal.

Recent Revelations from EAE: Surprising Roles for Starvation, Stress, and Cholesterol Metabolism. Leptin, a molecule that is critical in the regulation of energy balance and body weight, is a strong regulator of Th1 autoimmunity, as demonstrated by its potent influence on EAE (12, 13, 14). This is one of many examples of redundancy and overlapping roles of molecules within neuroendocrine systems and the immune system: for example, it had been shown that corticotropin releasing factor (CRF), a master regulator of hypothalamic and pituitary function, has an autonomous effect on the immune system. CRF can down-regulate Th1 autoimmunity, and block EAE (15). The neuroendocrine system can have potent effects on the immune system: basic behaviors like fasting have potent influences on the induction of Th1 autoimmunity. A short fast can circumvent an attack of autoimmune paralysis in EAE (13). Thus, while "feeding a cold" may have salutary effects on combating a viral infection, starving an autoimmune disease, exemplified by EAE, may protect against immune damage.

While "simple" acts like fasting influence immunity, complicated states like pregnancy modulate autoimmune diseases, as strongly as any known drug (16). Gender itself has an impact on autoimmunity, females being far more susceptible than males to diseases like systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis, and multiple sclerosis (4). In EAE female mice are far more susceptible to disease than males. Pregnancy amazingly ameliorates EAE (4), while genes associated with pregnancy are found in MS lesions (8). Interestingly, females produce more leptin than males (13). This may in part account for the increased susceptibility of females to many organ specific autoimmune diseases, like MS and rheumatoid arthritis.

In EAE we witness the remarkable choreography of molecules related to body weight and energy metabolism and the parallel roles of these same molecules in the finely tuned immune response. Studies in EAE have opened an interesting frontier in our understanding of how the brain influences the immune system. Another molecule HMG-CoA reductase is also modulated in MS brain. Recent evidence indicated that statins, inhibitors of HMG-CoA reductase, and the fundamental class of drugs used to lower cholesterol, may act to block the inductive expression of the class II major histocompatibility molecules. Earlier studies by McDevitt and colleagues had shown that blockade of MHC class II was effective in reversing EAE (17). Statins have now been shown remarkably to block ongoing paralysis and relapses in EAE, and to promote Th2 immunity. Increased phosphorylation of the transcription factor for Th2 cytokines, Stat 6, as well as decreased expression of MHC class II molecules in MS brain are consequences of oral administration of statins. Preliminary trials are underway in patients with MS, based on these preclinical results in mice with EAE (18).

EAE Provides a System To Test for New Therapies of Autoimmunity and Perhaps Vaccine Complications. EAE has served as a useful tool for the preclinical testing of new approaches to Th1 autoimmunity. Those therapies which actually reverse established EAE have shown some promise in the clinic. Perhaps most noteworthy has been the development of the random copolymer of tyrosine, glutamate, alanine, and lysine, with the relative concentrations of the amino acids formulated to resemble that of myelin basic protein. First invented by Teitelbaum, Arnon, and Sela at the Weizmann Institute the drug was shown to block EAE oral administration of statins. Preliminary trials are underway in patients with MS, based on these preclinical results in mice with EAE (18).

Table I. Similarities between Experimental Encephalomyelitis and Multiple Sclerosis

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<th>EAE</th>
<th>MS</th>
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<tr>
<td>1. Genetic susceptibility</td>
<td>Strong association with MHC class II</td>
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<tr>
<td>2. Environmental triggers</td>
<td>Strong association with prior infection</td>
<td>+ +</td>
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<tr>
<td>3. White matter pathology</td>
<td>Predominance of Th1 T cells in lesions</td>
<td>+ +</td>
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<td>4. Grey matter pathology</td>
<td>Axonal degeneration</td>
<td>+ +</td>
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<tr>
<td>5. Clinical presentation</td>
<td>Optic neuritis common in initial attack</td>
<td>+ +</td>
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<tr>
<td>6. Clinical forms</td>
<td>Relapsing/remitting, progressive forms</td>
<td>+ +</td>
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<tr>
<td>7. Clinical progression</td>
<td>Osteopontin important in progression</td>
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of relapse. More recently α4 integrin antibodies, shown to block the migration of T cells into the brain in EAE (20), has shown promise in controlled trials for multiple sclerosis and for inflammatory bowel disease (21). Antegren reduces the frequency of relapses and reduces activity on magnetic resonance brain scans (21).

The world is now confronting the specter of bioterrorism. Acute disseminated encephalomyelitis (ADE) after smallpox immunization (2) is one reason that vaccination programs are considered with fear and trepidation. Given the number of countermeasures to reverse EAE, perhaps we should be investing more resources on measures to predict who might be susceptible to such complications, and how to deal with such complications when they occur. Large scale proteomic approaches to monitoring autoimmune responses to central nervous system antigens (22), are in development and may offer at least a practical system for assessing who might become at risk for ADE.

The EAE model might be completely renamed NSRV, neurological syndrome referable to vaccination. In this context, the latest version of this EAE, acute optic neuritis described by Bettelli and colleagues (3) provides a test system for investigating one of the most common clinical presentations of an adverse reaction to routine vaccination. The latest revelation gained from studying EAE, a model for optic neuritis, demonstrates the utility of EAE over a period of time that has spanned the Great Depression, World War II, the discovery of the double helical nature of DNA, and now the unfortunate and chilling specter of bioterrorism. EAE may be there to help.

Figure 1. In EAE T lymphocytes gain access to the CNS via their α4 integrins, recognizing VCAM on the blood vessel wall (references 4, 20, and 21). The T cells diapedes through the endothelium, using matrix metalloproteases to cleave collagen IV in the extracellular matrix (reference 4). Once within the CNS they release inflammatory cytokines. The B cell and the mast cell also contribute to pathology (reference 4). Complement plus antibody leads to activation of membrane attack complexes which attack the myelin sheath (reference 4). EAE can be blocked by an α4 integrin antibody (reference 20). Antegren which recognizes human α4 integrin has shown promise in phase II trials in MS (reference 21). Statins (reference 18) and altered peptide ligands (references 51 and 52) can interfere with the recognition of myelin fragments by inducible MHC class II in the CNS (reference 4). Antihistamines and platelet activating receptor antagonists can block mast cell activity in EAE (reference 6).
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ceptor on T cells and thereby modulate autoimmunity demonstrated that it was possible to immunize against the re-
Salk Institute in its earliest days (29). Irun Cohen and Hart-
renowned for his work on poliomyelitis, engaged in re-
Jonas Salk, while Stan Prusiner was involved in the cloning of myelin
(Charles Janeway studied the role of adhesion molecules
mice, has created a T cell receptor modified lymphocyte
that triggers a Th2 response and modulates EAE, in his lat-
Howard Weiner and Caroline Whitacre have pioneered approaches to harness mucosal
immunity and guide it toward a platform to induce tolerance (23). The global nature of work on EAE is well known and includes Yamamura’s work on the role of NK cells in EAE (47), and the work of Claude Bernard, Ann Cross, Claude Genain, and Steve Hauser on the role of antibodies to MOG in demyelinating disease (48, 49). Cedric Raine has discovered that there is injury to the underlying axon, mediated in part by glutamate, in the degenerative phase of EAE (50, 51). Tak Mak, Hans Acha-Orbea, and Joan Goverman have made important observations on the role of ETA-1 in autoimmunity (9, 42). Jack Strominger has refined the use of peptides that interact with MHC molecules as a means for improving therapies for autoimmunity (33). Len and Lee Herzenberg demonstrated at about the same time as Don Mason and Steve Brostoff (34, 35), that CD4 T cells were critical in inducing autoimmune demyelination. The Herzenbergs and Vernon Oi, employed the then emerging technologies of monoclonal antibodies to target these T cells, including the creation of chimeric monoclonal antibodies, selecting for rare isotype switch variants using flow cytometry, or engineering the chimeric molecules (35, 36). Leroy Hood, who was the first to clone myelin basic protein along with Stan Prusiner (25), established a TCR transgenic model of disease (37).

Charles Janeway studied the role of adhesion molecules in lymphocyte migration to the CNS (20, 38). Marc Feldmann has extended to the realm of EAE and MS, his elegant work on blocking cytokines, work that has lead to a revolution in therapy for rheumatoid arthritis (39). Eli Sercarz reported the phenomenon of epitope spreading for the first time in EAE (40). Ethan Shevach studied the role of CpG motifs in DNA in the modulation of EAE (41). The CpG motifs contained in the mycobacteria that comprise Freund’s adjuvant were probably the key in Kabat’s early experiment (26). Harvey Cantor used the EAE model to describe the role of ETA-1 in autoimmunity (9, 42). Stephen Miller has applied his earlier work on tolerance induction with covalently coupled antigen done with Henry Claman to advance the studies to EAE, where he is inducing tolerance on a broad front (43), while Halina Offner, Art Vandenbark, and Jingwu Zhang have continued their efforts to target rogue T cells with sophisticated vaccination techniques (44, 45). Richard Flavell, who has used the EAE model in many of his clever genetically engineered mice, has created a T cell receptor modified lymphocyte that triggers a Th2 response and modulates EAE, in his latest creative effort (46).}

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<td>13. Horror Autoxicus and Anti-histamines in EAE by Pedotti and Teuscher 2001</td>
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Table II. Time Line of EAE: Some Highlights of the First 70 Years

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Michael Sela and Ruth Arnon pioneered synthetic approaches to the treatment of EAE, culminating in one of the two types of drugs now approved for immunotherapy of MS, Copaxone (19). Hugh McDevitt used the model to demonstrate that peptide based therapeutics aimed at the MHC could serve as an effective therapeutic approach (31, 32). Jack Strominger has refined the use of peptides that interact with MHC molecules as a means for improving therapies for autoimmunity (33). Len and Lee Herzenberg demonstrated at about the same time as Don Mason and Steve Brostoff (34, 35), that CD4 T cells were critical in inducing autoimmune demyelination. The Herzenbergs and Vernon Oi, employed the then emerging technologies of monoclonal antibodies to target these T cells, including the creation of chimeric monoclonal antibodies, selecting for rare isotype switch variants using flow cytometry, or engineering the chimeric molecules (35, 36). Leroy Hood, who was the first to clone myelin basic protein along with Stan Prusiner (25), established a TCR transgenic model of disease (37).
Coffinan and Jonathon Sedgwick at DNAx, who have extended the map of the Th1/Th2 paradigm on to the landscape of EAE (54). Scores of young investigators working with these leaders in the field of immunology and working independently established their research careers pursuing studies on this durable model.

“Many Rivers to Cross but Just Where to Begin.” Perhaps drawing on Thomas River’s name, we can think of EAE in the context of the reggae ballad, “Many Rivers to Cross” by Jimmy Cliff. What started out as a rigorous experimental attempt to reproduce one of the dreaded complications of infection and vaccination, has now enriched our understanding of this phenomenon, and has lead to the development of new therapies for the major autoimmune disease of the brain and spinal cord. In this world now facing the threat of bioterrorism it is worth remembering that Rivers, Sprunt, and Berry made a very salient observation predicting a strategy that could defuse the risk of horrendous neurological complications of vaccination: “We did find, however, that the brain of a monkey vaccinated on the skin rapidly becomes refractory to the active agent placed in the cisterna magna and the parietal lobe.” This deviation of an autoimmune response, via immunization with a similar, or slightly altered antigen, via another route is worthy of attention not only as a countermeasure for disseminated encephalomyelitis, but as a treatment for MS itself (55, 56). The EAE model is robust at age 70, and it would not be surprising to see that it is still serving as a model system for understanding autoimmunity when it reaches its 100th birthday in 2033.

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References

