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 discovered such models in a transgenic mouse with TCRs recognizing the major encephalitogenic epitope of myelin oligodendrogial 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 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 of optic neuritis than neurologists, for the obvious reason that patients and referring physicians turn to ophthalmologists first. In some cases there is optic neuritis with no 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 a peptide 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 and Fig. 1). 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 inducing EAE with features that include eosinophilic inflammation, sometimes also present in MS (7). Furthermore mast cells are present in MS lesions, and they secrete eosinophilic factors that may contribute to the development of EAE (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. Elimination must now be viewed as encompassing elements of metrically opposite to allergy. The pathogenesis of demyelination presents a challenge to our understanding of the pathophysiology of these disorders, previously thought to be dias- toimmunity and Perhaps Vaccine Complications. EAE has served as a useful tool for the preclinical testing of new approaches to Th1 autoimmunity. Those therapies which acted on December 25, 2017 jem.rupress.org Downloaded from

| Table I. Similarities between Experimental Encephalomyelitis and Multiple Sclerosis |
|---------------------------------|----------------------------------|------------------|
| Genetic susceptibility          | Strong association with         | MHC class II     |
| Environmental triggers          | Strong association with         | prior infection  |
| White matter pathology          | Predominance of Th1             | T cells in lesions |
| Grey matter pathology           | Axonal degeneration             | + +              |
| Clinical presentation           | Optic neuritis common           | + +              |
| Clinical forms                  | Relapsing/remitting,            | progressive forms |
| Clinical progression            | Osteopontin important           | + +              |

EAE MS

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 inducible 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 (19). The drug advanced through clinical trials over a period approaching 20 years, and is now an approved drug for multiple sclerosis, because of its ability to diminish the rate...
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.

EAE Has Attracted Many of the Best and the Brightest. My colleague Howard Weiner, who himself has contributed to our understanding of mechanisms of tolerance in EAE, estimated that nearly 5,000 papers have been written using the EAE model since its inception (23). Sometimes one is inclined to think that the best science and the best scientists work on C. elegans, zebrafish, or Drosophila. The EAE model has attracted some of the most influential immunologists of the last seventy years: two Nobel Prize winners in Medicine and Physiology, including Susumu Tone-
cepter on T cells and thereby modulate autoimmunity demonstrated that it was possible to immunize against the re-
munomodulation with Peptide Polymers by Sela and Arnon 1971

The Autoimmune Encephalomyelitis Era
7. Description of Epitope Spreading by Sercarz and Lehmann 1992
8. Role of Adhesion Molecules in EAE by Yednock, Karin, Steinman 1992
9. Creation of T Cell Receptor Transgenic by Hood and Goverman 1991
10. Transfer of EAE with Lymph Node Cells by Paterson 1960
11. Role of Adhesion Molecules in EAE by Yednock, Karin, Steinman 1992
12. Axonal Degeneration and Glutamate Toxicity by Raine 2001
13. Horror Autoxicus and Anti-histamines in EAE by Pedotti and Teuscher 2001

The Allergic/Autoimmune Encephalomyelitis Era
12. Axonal Degeneration and Glutamate Toxicity by Raine 2001
13. Horror Autoxicus and Anti-histamines in EAE by Pedotti and Teuscher 2001

The Allergic Encephalomyelitis Era
1. Establishment of the Model by Rivers 1933
2. Use of Freund’s Adjuvant by Kabat for Ease of Induction 1947
3. Transfer of EAE with Lymph Node Cells by Paterson 1960
4. The Role of the Thymus in EAE by Waksman 1962
5. Immunomodulation with Peptide Polymers by Sela and Arnon 1971

Charles Janeway studied the role of adhesion molecules in lymphocyte migration to the CNS (20, 38). Marc Feld-ermann has extended to the realm of EAE and MS, his ele-
gant work on blocking cytokines, work that has lead to a revolution in therapy for rheumatoid arthritis (39). Eli Ser-
carz 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).

Industry has made important advances with this model, particularly Robert (30). 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 in-
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gawa (7) and Peter Doherty (24) have worked on EAE, while Stan Prusiner was involved in the cloning of myelin basic protein (25). Tonegawa showed that Th2 T cells could induce EAE in some instances (7), while Doherty worked on the role of iron chelators in regulating EAE (24). Elvin Kabat first used the adjuvant invented by Jules Freund to induce EAE with a single injection in monkeys (26). Byron Waksman established the roles of inflammatory cytokines in autoimmunity, and the role of the thymus using this model (27). Phil Paterson demonstrated that cells could transfer the disease, not antibodies (28). Jonas Salk, renowned for his work on poliomyelitis, engaged in research on myelin basic protein in EAE with Ed Eylar at the Salk Institute in its earliest days (29). Irun Cohen and Hartmut Wekerle, along with their student avi Ben-Nun, demon-


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 autoimmunity using EAE, and showed that factors in the environment were a key trigger for induction of clinical disease (37).

industry to 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 demonstrated 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 CD8+ T cells in EAE (52, 53). Industry has made important advances with this model, particularly Robert
Coffin 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

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