

## Thomas Rivers and the EAE model

**In the early 1930s, Thomas Rivers and colleagues provided the first evidence that immune cells can attack the brain. Their simple experiments established what is now the most well-studied model of autoimmunity—the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis.**

Early vaccinations against viral diseases such as rabies occasionally resulted in “paralytic accidents”—central nervous system (CNS) complications in which inflammatory cells invaded the brain and demyelinating lesions ensued (1). These complications were widely attributed to an incomplete inactivation of the vaccine virus, which was grown in rabbit brain tissues. But there was another possible explanation: repeated injections of brain tissue might have triggered an allergic reaction.

### Rabbit brains and Rhesus monkeys

Studies had shown that injection of foreign brain tissues into the brains of rabbits could cause paralysis (2). Intrigued, Rivers—then a virologist at The Rockefeller Institute—set out to duplicate these studies in monkeys. Rivers and his colleagues injected Rhesus macaques with normal brain extracts from rabbits and showed that most of the monkeys developed acute CNS disease with immune cell infiltration and demyelinating lesions. No infectious agent could be cultured from the animals, putting to rest suspicions of an infectious etiology. Rivers’ group also noted that the disease-inducing capacity of the brain extracts paralleled their myelin content, providing the first hint that myelin was involved in disease induction. Thus, the experimental allergic (now “autoimmune”) encephalomyelitis (EAE) model was born. The group published these observations in three articles in the *Journal of Experimental Medicine* (3–5).

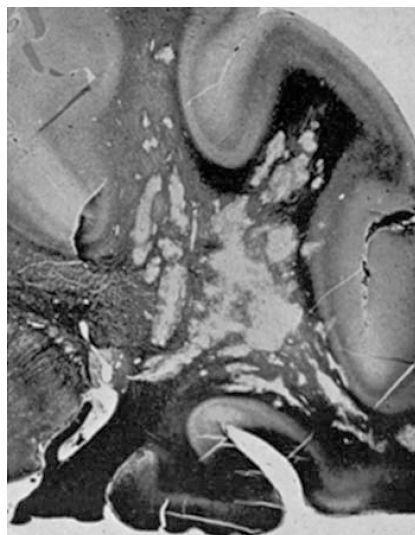
### Time-saving measures

Rivers’ groundbreaking experiments were cumbersome and time consuming, requiring multiple injections (up to 85 per animal) over a period of a year. Elvin Kabat (Columbia University) later

fast-tracked the disease process by combining brain extracts with the adjuvant recently developed by Jules Freund. This combination induced disease after only a single injection (6). Another important finding made by Kabat’s group and also by Isabel Morgan (Johns Hopkins University) was that disease could be reproduced using brain extracts from genetically homologous monkeys—the first indication that an autoimmune process was at work (6, 7).

### Deciphering mechanisms

Kabat—who was probably the first to note the similarities between EAE and MS—had speculated that antibodies specific for the injected brain material were to blame for the disease. Over a decade later, however, T cells emerged as the primary instigators of EAE. The transfer of spleen cells, but not antibody, triggered the CNS disease in rats (8), and removal of the thymus from newborn rats prevented the development of EAE later in life (9). Thanks to decades of research conducted by an impressive cast of char-



Demyelination in the parietal lobe of a Rhesus macaque. Image reproduced from Rivers et al. (3).

acters (for review see reference 10), the pathology of EAE is now known to involve multiple aspects of the immune response including CD4<sup>+</sup> T cells, antibodies, complement, and chemokines.

### EAE branches out

Many versions of the EAE model now exist, which vary both in the strategies used to evoke disease and in the resulting pathology. Critics of the EAE model question whether this animal model is truly reflective of human MS, as many EAE models trigger a specific acute syndrome, whereas most human disease involves cycles of relapse and remission. Vijay Kuchroo (Harvard University) defends the EAE model, pointing out that “each model recapitulates a small piece of the human disease,” and has provided valuable insights into the human disease. Lawrence Steinman (Stanford University) seconds Kuchroo’s sentiments, adding, “To say that EAE has little to do with MS would be to ignore that two approved treatments for MS [Copaxone and Tysabri] were developed as a result of experiments in the EAE model.”

The EAE model has also shaped the modern day evaluation of vaccines by contributing to the understanding of how a vaccine, independent of the organism it is intended to generate immunity against, can sometimes have devastating side effects.

### REFERENCES

1. Stuart, G., and K.S. Krikorian. 1928. *Ann. Trop. Med. Parasitol.* 23:327–377.
2. Hurst, E.W. 1932. *J. Hyg.* 32:33–44.
3. Rivers, T.M., D.H. Sprunt, and G.P. Berry. 1933. *J. Exp. Med.* 58:39–56.
4. Schwentker, F.F., and T.M. Rivers. 1934. *J. Exp. Med.* 60:559–574.
5. Rivers, T.M., and F.F. Schwentker. 1935. *J. Exp. Med.* 61:689–705.
6. Kabat, E.A., A. Wolf, and A.E. Bezer. 1946. *J. Exp. Med.* 85:117–130.
7. Morgan, I.M. 1947. *J. Exp. Med.* 85:131–140.
8. Paterson, P.Y. 1960. *J. Exp. Med.* 111:119–133.
9. Arnason, B.G., B.D. Jankovic, B.H. Waksman, and L. Wennerstein. 1962. *J. Exp. Med.* 116:177–186.
10. Steinman, L. 2003. *J. Exp. Med.* 197:1065–1071.

Text by Heather L. Van Epps  
JEM News Editor; hvanepps@rockefeller.edu