Response to Comment on "Critical Roles of NK and CD8+ T Cells in Central Nervous System Listeriosis"

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*J Immunol* 2009; 183:5437-5438;
doi: 10.4049/jimmunol.0990086

http://www.jimmunol.org/content/183/9/5437.2

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With interest we noticed the article by Hayashi et al. in the May 15, 2009 issue of *The Journal of Immunology* (1). The authors reported the injection of *Listeria* into the ventricular system resulting in lethal “ventriculitis,” whereas injection into the brain parenchyma induced nonlethal meningoencephalitis. However, histopathology shows that Hayashi et al. induced brain abscess instead of meningoencephalitis by intraparenchymal injection (Fig. 2A of Ref. 1) and ventriculitis plus periventricular encephalitis by ventricular infection (Fig. 2F of Ref. 1), respectively.

The authors stress that their “encephalitis” model serves as a model for human cerebral listeriosis superior to the “ventriculitis” model claimed to be used by us. However, we (2–4) and others (5–7), whose pioneering work, unfortunately, escaped citation by Hayashi et al. (1), studied the course of disease upon injection of bacteria into the forebrain but not into the ventricular system. Under these conditions, ventriculitis starts in the fourth ventricle, which is far distant from the injection site (2). Thus, panels C–E in Fig. 1 of Ref. 1, which appear to be intended to explain our model of cerebral listeriosis but surprisingly are not explained in *Materials and Methods* and Results (1), are incorrect.

Hayashi et al. also show that infection with $3 \times 10^3$ *Listeria* induces lethal cerebral listeriosis after injection into the brain parenchyma (Fig. 4A of Ref. 1), further refuting their conclusion that the anatomic site of infection is the major factor determining the course of cerebral listeriosis.

Hayashi et al. (1) question the use of recombinant and attenuated *Listeria* in experimental listeriosis. However, genetically manipulated *Listeria* are extremely helpful in analyzing the immunology and pathogenesis of systemic and cerebral listeriosis (8–10).

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**References**


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We appreciate the comments by Drs. Deckert and Schlüter on our paper entitled “Critical roles of NK and CD8+ T cells in central nervous system listeriosis” (1). Although they emphasize the difference between meningoencephalitis and brain abscess, brain abscess is one of specific states of meningoencephalitis that develops within the brain parenchyma (2). Ventriculitis is usually accompanied by periventricular encephalitis, which was also observed in our model of ventriculitis. We accept the criticism that our encephalitis model by intraparenchymal injection may not be an ideal model for human encephalitis induced by natural infection of *Listeria*. Because we appreciate the work by Drs. Deckert and Schlüter, we cited six of their reports in our paper. We understand that they injected bacteria into the right caudate nucleus as they described in their paper (3, 4), it is quite difficult to limit the bacterial inoculation point. Second point is in regard to the lethal dose of bacteria.
A lethal dose of bacteria varies depending on mouse strains and bacterial culture conditions. As shown in our paper, wild-type BALB/c mice were able to survive upon intraparenchymal infection of $3 \times 10^2$ CFU of *Listeria*, which was below the lethal dose of *Listeria* culture that we prepared. Our results showing that infection of $3 \times 10^2$ CFU of *Listeria* induces nonlethal CNS listeriosis and that $3 \times 10^3$ *Listeria* results in a lethal outcome do not refute the conclusion that the anatomic site of infection is the major factor determining the course of cerebral listeriosis. Their third point concerned the use of recombinant and attenuated *Listeria* in experimental listeriosis. We do not question the use of recombinant and attenuated *Listeria*. We understand that such strains are useful to examine the mechanisms of bacterial pathogenicity and virulence (5). Attenuated strains usually lack some of virulence factors that enable bacteria to escape host immune response. To examine the function of immune system, it was ideal to use wild-type bacteria. Indeed, we did not need to use attenuated bacteria.

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www.jimmunol.org/cgi/doi/10.4049/jimmunol.0990086