We conclude that it is premature to suggest that murine γHV-induced vasculitis is an animal model for human vasculitis

YOSHIKAZU YONEMITSU
Ion Transport Unit
National Heart and Lung Institute
Imperial College School of Medicine
Manresa Road, London, SW3 6LR
email y.yonemitsu@ic.ac.uk

Virgin et al. reply—The author concludes his letter by stating that "it is premature to suggest that murine γHV-induced vasculitis is an animal model for human vasculitis." It should be noted that our work is a proof of principle that a class of viruses (γ- herpesviruses) can cause inflammatory disease of the great vessels. Clearly, definitive experiments for human disease have not yet been completed. Thus, whereas we appreciate Dr. Yonemitsu's opinion, we feel that researchers in the field need to keep an open mind.

With respect to the presence of HCMV in some human arteritic lesions, the papers referred to by Yonemitsu provide support for the presence of HCMV transcripts in inflammatory human aortic lesions (but not classical atheromatous lesions)[3,5]. Although we referenced an earlier paper implicating HCMV in inflammatory arteritis[4], we were unaware of the other papers. The issue of whether HCMV is directly responsible for the lesions, or is merely replicating in lesions generated by some other insult, has not yet been addressed. Furthermore, the relationship between these inflammatory aortic lesions and classical atherosclerosis remains to be fully evaluated. Nevertheless, demonstration of HCMV RNA in human vascular lesions is an important observation, and we appreciate the author bringing these papers to our attention.

That the author's focus on the importance of the HCMV-IE transcripts that have been detected in arteritic lesions seems premature when transcription from other regions of the viral genome has not been examined. The fundamental question of whether HCMV is lytically replicating or is latent, or both, in the lesions, has not yet been addressed. Transcription from the IE region is complex. The IE region is also transcribed in lytically infected cells. However, although controversy exists[7], recent studies demonstrate that the IE region is transcribed in latent cells as well[8]. The HCMV transcripts present in inflammatory aortic lesions have not been defined, and protein from these transcripts has not yet been detected. Products of the IE locus may have many important roles in addition to regulation of smooth muscle cell proliferation including regulation of the extent of viral replication, apoptosis, and transcription of host and viral genes.

With regard to the other points raised by Yonemitsu, we are unclear why he reviews Koch's postulates, which we have fulfilled in the case of γHV68 and the induction of arteritis in IFN-γ unresponsive mice. We also feel that the presence of perforin positive cells in the lesions we observe would not be a strong argument for a relationship to human disease. Perforin positive cells would be expected in any lesion containing activated NK cells or $CD8^+$ T cells. Finally, as stated by Yonemitsu, the obvious extension of the mouse model would be the identification of a γ-herpesvirus in human arteritic lesions. This could either be one of the two known human γ-herpesviruses, or an as yet unidentified member of this family. It should also be noted that the possible association of HCMV with some human arteritic lesions in no way addresses the possible role of a γ-herpesvirus as an etiologic agent of human arteritis.

SAMUEL H. SPECK &
HERBERT W. VIRGIN
Depts. of Pathology and Molecular Microbiology
Washington University School of Medicine
Box 8118, 660 South Euclid Ave
St. Louis MO 63110
email: virgin@immunology.wustl.edu

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