

# This Week's Citation Classic®

**Klemola E & Kääriäinen L.** Cytomegalovirus as a possible cause of a disease resembling infectious mononucleosis. *Brit. Med. J.* 2:1099-102, 1965; and **Kääriäinen L, Klemola E & Paloheimo J.** Rise of cytomegalovirus antibodies in an infectious-mononucleosis-like syndrome after transfusion. *Brit. Med. J.* 1:1270-2, 1966.

[Dept. Virol., Univ. Helsinki; Aurora Hosp.; and First Dept. Med., Univ. Central Hosp., Helsinki, Finland]

A significant rise in titer of antibodies to cytomegalovirus was established during the disease in five previously healthy individuals with a mononucleosis-like disease without a positive heterophil agglutination test. A similar disease, "cytomegalovirus mononucleosis," was demonstrated in three patients after transfusion. [The *SCI*® indicates that these papers have been cited in more than 265 and 215 publications, respectively.]

## A New Disease for an Old Virus

Leevi Kääriäinen  
Institute of Biotechnology  
University of Helsinki  
SF-00380 Helsinki  
Finland

In January 1965, I was working at the Department of Virology, University of Helsinki, Finland, as a young assistant. I was finishing my PhD thesis on a tick-borne encephalitis virus when my brother-in-law called me on January 19 and told me that he had been suffering from a febrile disease with intensive vertigo and weakness for close to two weeks. I sent him for laboratory tests, which showed lymphocytosis with atypical lymphocytes in the presence of mild leucocytosis. At the same time, a serum sample was taken. I anticipated that the patient might have infectious mononucleosis and contacted Erkki Klemola, an enthusiastic specialist of infectious diseases at the Aurora Hospital in Helsinki. We had previously published two papers concerning the etiology of viral meningitis. Klemola had some doubts about my "diagnostic criteria," but he considered the state of the patient serious enough to warrant hospitalization. The disease was rather persistent, with severe vertigo and fever. The heterophil agglutination test was negative, contradicting the diagnosis of classical infectious mononucleosis. As I had been developing routine diagnostics in virus serology, I wanted to apply it to this interesting case of mine.

Four serum samples within a period of one month were taken from the patient and complement-fixing antibodies against 20 different viruses were determined. There was a highly significant rise of antibodies only to cytomegalovirus (CMV). Now, Klemola got really interested and started to look for similar patients at the Aurora Hospital.

Within a few months, we had five patients with a negative heterophil agglutination test and a significant rise in CMV antibodies. At the same time, we were running hundreds of control sera, almost occluding our diagnostic service. The paper was sent for publication to the *British Medical Journal* where it was published in November 1965.

The clinical picture of a febrile disease after massive transfusion in open-heart surgery was very similar to our newly found atypical mononucleosis. We soon found a patient who had received a large amount of fresh blood after a gynecological operation. She had developed an atypical mononucleosis with a significant rise in antibodies against CMV. Two similar cases after open-heart surgery convinced us that CMV was the causative agent of a mononucleosis-like disease in healthy adults as well as in patients subjected to massive transfusions of fresh blood. In the above article, published in May 1966, we suggested "cytomegalovirus-mononucleosis" as the name for the disease. Soon we isolated CMV from a patient subjected to open-heart surgery<sup>1</sup> and showed that subclinical infections were also common after massive transfusions.<sup>2</sup> The number of CMV-mononucleosis cases with additional interesting features rose rapidly due to the effective research by Klemola and his colleagues.<sup>3,4</sup>

This contact with active and enthusiastic clinicians was interrupted by my postdoctoral visit to the Sloan-Kettering Institute for Cancer Research, New York, where I started serious studies on molecular virology. After that I have remained faithful to togaviruses, studying now the functions of the nonstructural proteins of Semliki Forest virus.<sup>5</sup>

1. Kääriäinen L, Paloheimo J, Klemola E, Mäkelä T & Koivuniemi A. Cytomegalovirus-mononucleosis. Isolation of the virus and demonstration of subclinical infections after fresh blood transfusion in connection with open-heart surgery. *Ann. Med. Exp. Biol. Fenn.* 44:297-301, 1966. (Cited 80 times.)
2. Paloheimo J A, Von Essen R, Klemola E, Kääriäinen L & Siltanen P. Subclinical cytomegalovirus infections and cytomegalovirus mononucleosis after open heart surgery. *Amer. J. Cardiol.* 22:624-30, 1968. (Cited 100 times.)
3. Klemola E, Weckman N, Haltia K & Kääriäinen L. The Guillain-Barré syndrome associated with acquired cytomegalovirus infection. *Acta Med. Scand.* 181:603-7, 1968.
4. Klemola E, Kääriäinen L, Von Essen R, Haltia K, Koivuniemi A & Von Bonsdorff C-H. Further studies on cytomegalovirus mononucleosis in previously healthy individuals. *Acta Med. Scand.* 182:311-22, 1967. (Cited 80 times.)
5. Peränen J, Rikonen M, Liljeström P & Kääriäinen L. Nuclear localization of Semliki Forest virus-specific nonstructural protein nsP2. *J. Virol.* 64:1888-96, 1990.

Received November 21, 1990