



# HOKKAIDO UNIVERSITY

Title	Laoratory of Public Health (An Introduction of the four Departments composing the Graduate Scholl of Veterinary Medicine, Hokkaido University (2))
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Citation	Japanese Journal of Veterinary Research, 45(3), 176-177
Issue Date	1997-11-28
Doc URL	<a href="https://hdl.handle.net/2115/2607">https://hdl.handle.net/2115/2607</a>
Type	departmental bulletin paper
File Information	KJ00002398567.pdf



## Laboratory of Public Health

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History: The Laboratory of Public Health was established in 1952 when the Faculty of Veterinary Medicine was separated from the Faculty of Agriculture. In the years under the first Professor, the late Dr. S. Hamada, food hygiene was the major subject of research. As a pioneer in milk hygiene, he contributed in the improvement of the quality of milk and milk products.

From 1977, former Professor, Dr. N. Hashimoto took charge of the laboratory and zoonoses were the subject of the research. The primary subjects of interest were Japanese encephalitis, chlamydiosis, Yersiniosis and hantavirus infection which were zoonoses of major importance. Development of diagnostic tests and performance of epidemiological surveillance contributed greatly to the prevention of these zoonoses.

From 1996, present Professor, Dr. I. Takashima assumed charge of the laboratory with aid from Assistant professor, Dr. H. Kariwa and Instructor, Dr. T. Mizutani. As research subjects, we have selected major viral zoonoses which are currently causing serious problems in Japan and Asia. We are engaging in the development of diagnostic tests, epidemiological survey, and elucidation of the transmission cycles in several viral zoonoses as described below.

Tick-borne encephalitis; In 1993, an encephalitis patient was diagnosed as having Russian spring summer encephalitis (one subtype of tick-borne encephalitis) in the Oshima district of Hokkaido. Tick-borne encephalitis had not previously been described in Japan. Russian spring summer encephalitis is a serious viral zoonoses transmitted by *Ixodes* ticks and the mortality rate reaches 50% in some outbreaks. Several

thousand patients of tick-borne encephalitis are reported annually in Europe and north Asia.

We isolated several strains of tick-borne encephalitis virus from sentinel dogs, *Ixodes ovatus* ticks, and rodents in the study area where the patient was found. We proved the endemic foci distribution was over a wider area of Hokkaido. The isolated viruses were identified as Russian spring summer encephalitis subtype by nucleotide sequence analysis of envelope protein genes of the isolates. Studies are now under way for the further characterization of the virus isolates, vaccine development and elucidation of the origin of the virus.

Hantavirus infection; Hemorrhagic fever with renal syndrome is caused by hantavirus transmitted from rodents. We succeeded in virus isolation from rats in an epidemic of an infected animal laboratory facility. Using the isolated virus as antigen, we established the serological diagnostic test. By applying this diagnostic test, virus-infected rats were successfully eliminated from animal laboratory facilities in Japan. We found several endemic foci of hantavirus in wild rat populations in Japanese dumps. Several virus strains were isolated from wild rats and genetic characteristics of the isolates were examined. Mode of virus excretion and transmission were studied in naturally and experimentally infected rats. In wild rodent populations in Hokkaido, high antibody positive rates were detected at many survey points. Hantavirus genomes were amplified from lung tissues from antibody positive rodents. By determining the nucleotide sequences of the viruses, the prevalent viruses were found to be Puumala-type virus which is prevalent in Europe and causes the serious illness called Nephropatia Epidemica in many European countries. We are now examining serologically high risk groups of residents to find the rate of prevalence among humans in Hokkaido.

Borna disease : Borna disease in horses has

been known as a chronic encephalomyelitis endemic to Germany and several other European countries. Natural infection of Borna disease virus (BDV) has been reported in other vertebrates. Furthermore, recent epidemiological studies have shown suggestive data that BDV may have some relation with neuropsychiatric disorders in humans. This is based on the findings of a higher prevalence of anti-BDV antibody and BDV-genome among psychiatric patients than among healthy individuals. In Japan, distributions of BDV have been reported among humans, horses, cattle, sheep and cats by means of antibody and viral genome detection. However, there has still been discrepancies of the survey results due to the lack of standardized diagnostic tests. We started to establish specific and sensitive diagnostic tests of Borna disease. As one test, we developed a single-tube RT-PCR which is equal in sensitivity to nested PCR to detect the BDV genome and minimize the risk of contamination which always accompanies nested PCR. We are now preparing monoclonal

antibodies which can be applied to an antigen detection system and for capturing antibody in antibody-detecting ELISA.

Publications (major) :

- 1) Takashima, I., Morita, K., Chiba, M., Hayasaka, D., Sato, T., Takezawa, C., Igarashi, A., Kariwa, H., Yoshimatsu, K., Arikawa, J. and Hashimoto, N. 1997. A case of tick-borne encephalitis in Japan and isolation of the virus. *J. Clin. Microbiol.*, 35 : 1943-1947.
- 2) Kariwa, H., Kimura, M., Yoshizumi, S., Arikawa, J., Yoshimatsu, K., Takashima, I. and Hashimoto, N. 1996. Mode of Seoul virus infections : persistency in newborn rats and transiency in adult rats. *Arch. Virol.*, 141 : 2327-2338.
- 3) Kariwa, H., Yoshizumi, S., Arikawa, J., Yoshimatsu, K., Takahashi, K., Takashima, I. and Hashimoto, N. 1995. Evidence for the existence of Puumala-related virus among *Clethrionomys rufocanus* in Hokkaido, Japan. *Am. J. Trop. Med. Hyg.*, 53 : 222-227.