1976: Lee Ho Wang's Discovery of the Etiologic Agent of Epidemic Hemorrhagic Fever

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One late night in 1976, inside a shabby laboratory in Hyehwa-dong, Seoul—its ceiling perforated and heated only by coal briquettes – Lee Ho Wang and his assistant Lee Pyung woo were deep in experiment. Adjusting the focus of a fluorescence microscope, they suddenly saw yellow fluorescent signals resembling the Milky Way appear on the specimen slide. It was the moment when the etiologic agent of Korean hemorrhagic fever, long sought by researchers worldwide, was finally identified. [Figure 1]

[Figure 1] Fluorescence microscope image of the hemorrhagic fever pathogen
Source: Courtesy of Lee Pyung woo

Korean hemorrhagic fever is a seasonal infectious disease occurring in spring and autumn, presenting initially with fever and headache, progressing to lower back pain, renal failure, hemorrhagic manifestations, and in severe cases, death. During the Korean War, the disease spread widely among U.S. troops near the demilitarized zone, at times prompting suspicion of biological warfare. Soviet, Japanese, and American researchers had each attempted to identify the causative pathogen—the U.S. Army even established a Hemorrhagic Fever Center in Korea and forwarded experimental materials to laboratories in Japan and Washington, D.C.—but all efforts ended in failure. It was under these circumstances that Lee Ho Wang entered the field.

Lee Ho Wang was born in Sinhung County, South Hamgyong Province. When the Korean War broke out during his studies at Hamhung Medical College, he fled to Seoul and, through the Wartime Union Universities system, transferred to Seoul National University College of Medicine, graduating in 1954. His decision to pursue graduate studies in microbiology was shaped by Professor Kee Ryong-sook's passionate teaching and by the many infectious diseases prevalent in Korea at the time.[1] While working as a teaching assistant, he was selected for study in the United

1) At that time, microbiology courses at Seoul National University College of Medicine were taught by Professor Kee Ryong-sook. In his memoirs, Lee Ho Wang recalled that, unlike other professors, Kee did not rely on blackboard-centered lectures; instead, he conducted discussion-based classes with active questions and answers and used audiovisual teaching methods, explaining concepts with bacterial experiment charts that he had produced himself.

States through the Minnesota Project,[2] where, despite early language barriers, he completed his doctorate at the University of Minnesota in 1959 with a dissertation on Japanese encephalitis virus immunity, mastering tissue culture techniques then at the cutting edge of virology.

After returning to Korea, Lee continued research on Japanese encephalitis with NIH funding. When news arrived from Japan that a vaccine had been successfully developed, he turned his attention elsewhere. During a visit to the Walter Reed Army Institute of Research, a colleague suggested epidemic hemorrhagic fever as a research subject. Lee recognized that his virological expertise and his position in Korea—where the disease actually occurred—made him uniquely suited to tackle the problem. Beginning in 1970, he launched research on epidemic hemorrhagic fever with support from the U.S. Army Medical Research and Development Command.

Drawing on prior Soviet, Japanese, and American studies, Lee selected three main experimental subjects: hemorrhagic fever patient sera, wild rodents, and ectoparasites. Using the tissue culture cell method he had mastered in the United States, he inoculated patient blood into porcine kidney, Vero, and HeLa cells, but the cytopathic effects were inconsistent and irreproducible. [Figure 2] Experiments with ectoparasites —ticks, fleas, and lice collected from rodents in outbreak regions—also failed; the most abundant species did not feed on blood, casting doubt on their role. Wild rodents proved more promising: Lee found that the striped field mouse (*Apodemus agrarius*) was most common overall, but the *Microtus fortis* appeared specifically in the northern Gyeonggi Province, where hemorrhagic fever was prevalent. Crucially, a team member who contracted hemorrhagic fever during field collection had handled *Microtus fortis* two to three weeks before onset, heightening suspicion of this species.

[Figure 2] Lee Ho Wang conducting an experiment on hemorrhagic fever
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Neutralization experiments with *Microtus fortis* yielded irregular results, and in 1973 collaborative analysis with Karl M. Johnson[3] revealed that the two promising viral strains were merely a reovirus and a herpesvirus, both unrelated to hemorrhagic fever. As tissue culture methods applied to all three subject categories produced no meaningful results, Lee pivoted to a new approach: measuring immunoglobulin (Ig)[4]

2) The Minnesota Project refers to an agreement between the University of Minnesota and Seoul National University, established with support from the International Cooperation Administration (ICA) for the purpose of postwar reconstruction in Korea. Through this project, exchange professor programs, facility restoration, and equipment support were provided to three colleges at Seoul National University: agriculture, engineering, and medicine.
3) Johnson was named a Clarivate Analytics Citation Laureate in 2021, alongside Lee Ho Wang.
4) Immunoglobulins are proteins produced in response to antigenic stimulation and function in antigen-antibody reactions in the blood. There are five types of immunoglobulins: IgG, IgA, IgM, IgD, and IgE.

levels in patient sera. His 1974-1975 experiments showed that IgD concentrations rose in recovering patients, IgM peaked around the twentieth day of illness, and IgG increased between the fourteenth and twentieth days—confirming that specific antibodies formed during the disease course. [Figure 3]

[Figure 3] Lee Ho Wang examining a patient with hemorrhagic fever
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To identify the antigen binding these antibodies, Lee adopted the fluorescent antibody technique—applying fluorescently tagged antibodies to tissues and observing reactions under a fluorescence microscope—recommended by Johnson during a 1973 laboratory visit. The method required specialized equipment and skills unfamiliar to the team; Lee therefore tasked assistant Lee Pyung woo with mastering it, with help from Choi Cheol-soon of the Veterinary Research Institute, who had studied the technique in Australia. By late 1974 the team was capable of conducting fluorescent antibody experiments. Beginning in 1975, Lee added lung tissue from wild rodents as an experimental material—previously excluded because it contains many contaminants and shows no visible lesions—after reading a book by William L. Jellison, which speculated that a pulmonary organism in rodents might be the causative agent. Though Lee dismissed the fungal hypothesis, he was struck by the localization in the lungs.

Applying the fluorescent antibody technique to wild rodent tissues, the researchers found specific reactions in nine lung and five kidney tissue samples from *Apodemus agrarius* collected in 1974, and in fourteen lung and four kidney samples from 1975. [Figure 4] Neutralization tests showed that the convalescent serum titer was more than four times higher than the acute-phase titer, confirming that antibodies in patient sera reacted specifically with antigens in *Apodemus agrarius* tissues and increased markedly as the disease progressed. This was the moment when the long-sought antigen was confirmed to exist—though, having experienced repeated failures, Lee chose to verify the findings rigorously. He repeated the experiments with quantitatively measured reagents and conducted blind tests in which normal and patient sera were randomly coded before examination; all patient sera reacting to the antigen were correctly identified.

[Figure 4] Apodemus agrarius
Wikipedia

Lee provisionally named the verified antigen the “Korea antigen” and announced the discovery at a press conference on April 29, 1976, just before the annual meeting of the Korean Association of Internal Medicine.[5] The announcement drew

5) While academic research is typically published in academic papers, this case is somewhat

skepticism both in Korea and abroad—the U.S. Army, whose funding was then in question, even suspected the results might be staged to secure continued support.[6] To dispel doubts, Lee traveled to the United States and reproduced the experiments there, then conducted repeated blind tests at the request of other researchers. He subsequently characterized the antigen's physicochemical properties as a virus and registered it under the name "Hantaan virus" in the catalog of the American Committee on Arthropod-borne Viruses, establishing himself as the first researcher in the world to identify the pathogen responsible for epidemic hemorrhagic fever.

Lee continued his research on hemorrhagic fever-like diseases in Korea and abroad, demonstrating the existence of the Seoul virus, developing the diagnostic kit Hantadia in collaboration with Japanese scientists (1989), and releasing the preventive vaccine Hantavax with Green Cross (1990). [Figure 5] Achieving the discovery of a novel virus alongside the development of both a diagnostic method and a preventive vaccine is an accomplishment rarely attained by virologists. Working from South Korea —then considered a latecomer in science—Lee established himself as a central figure in international research. In today's world, where humanity remains vulnerable to emerging infectious diseases, the significance of Lee Ho Wang's achievements deserves renewed recognition.

[Figure 5] Hantadia and Hantavax
Collection of the National Science Museum

unusual.

6) The year 1976, when the announcement was made, was also the time when Lee Ho Wang had been informed by the U.S. Army that continued research funding would be difficult to secure continuously. Under these circumstances, he likely felt the need to publicize his findings quickly and appears to have chosen the media as the means to do so.

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