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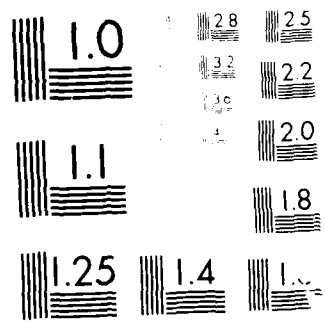
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HEMORRHAGIC FEVER WITH RENAL SYNDROME  
(KOREAN HEMORRHAGIC FEVER)

ANNUAL QUARTERLY REPORT

DR. WANG HUI, M.D.

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) <p>&gt; Hantavirus is ubiquitous in the world but total number of reported HFRS patient in Euro-Asia is about 200,000 with 5-7% mortality annually. Hemorrhagic fever with renal syndrome (HFRS) was an important military problem since large epidemics of HFRS occurred among soldiers in the many past wars and although predominantly associated with field mice in rural areas, it is now being recognized that urban wild and laboratory rats are also reservoirs of HFRS in many parts of the world.</p> <p>Therefore, seroepidemiological survey of distribution of hantaviruses and surveillance of occurrence of HFRS in the world are important for prevention of this highly fatal disease. It is also important to investigate antigenic differences of strains of hantavirus isolated from rats caught in non-endemic areas of the world because HFRS patient has never been documented in many areas despite our finding of positive rats there.</p>					
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The methods for diagnosis of HFRS, isolation of Hantaviruses from man and rodents, intraspecific transmission of Hantaviruses in rodents are described previously.

There were 706 cases of HFRS in Korea in 1986 and recently no. of HFRS patients are increasing in urban cities, and large epidemics of leptospirosis and scrub typhus were occurred during epidemic season of HFRS. Seroepidemiologic survey of wild rodent showed that 14% of 230 Apodemus mice and 30% of 157 house rats were seropositive against Hantavirus, 68% of 196 Apodemus mice, 6 out of 8 Microtus mice and 5% of 139 house rats were seropositive against R. tsutsugamushi, and 9% of 230 Apodemus mice, 3 out of 8 Microtus mice and 21% of 139 house rats were seropositive against L. interrogans. IFAT and Elisa are sensitive and rapid seroepidemiological tools for survey of HFRS and PRNT is specific test for serotyping of Hantavirus infection and IF, Elisa and PRN antibodies persisted 17 years after illness.

> A near global distribution of Hantavirus was demonstrated. HFRS patients infected with Seoul virus occurred in endemic and non-endemic areas of HFRS and the most characteristic clinical features are fever, headache, strong abdominal symptoms, hepatic dysfunction and mild renal dysfunction. Five strains of Seoul virus were isolated from urban rats caught in Hong Kong, and Singapore and the strains are a little different antigenically from prototype Seoul virus 88/89 by monoclonal antibody assay.

Abortion of a 8th month old fetus due to vertical transmission of Hantaan virus in a pregnant woman with HFRS was documented serologically and pathologically for the first time.

A

SUMMARY

In 1986, there were 706 cases of hospitalized HFRS patients diagnosed at our laboratory in Korea, and 166 and 10 patients were ROK Army and US Army soldiers, respectively. No. of HFRS patient in urban areas of Seoul is increasing every year.

Large epidemics of scrub typhus and leptospirosis were occurred during epidemic season of HFRS and numbers of patients confirmed at our laboratory were 215 and 64, respectively. Field mice and wild rats were reservoir hosts of HFRS, scrub typhus and leptospirosis. 14% of 230 Apodemus mice and 30% of 157 house rats were seropositive against Hantavirus, 68% of 196 Apodemus mice, 6 out of 8 Microtus mice and 5% of 139 house rats were seropositive against R. tsutsugamushi, and 9% of 230 Apodemus mice, 3 out of 8 Microtus mice and 21% of 139 house rats were seropositive against L. interrogans.

A near global distribution of Hantavirus was demonstrated. HFRS patients infected with Seoul virus occurs in endemic and non-endemic areas of HFRS and the most characteristic clinical features are fever, headache, strong abdominal symptoms, hepatic dysfunction and mild renal dysfunction. Five strains of Seoul virus were isolated from urban rats caught in Hong Kong and Singapore and the strains are a little different antigenically from prototype Seoul virus 80/39 by monoclonal antibody assay.

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FOREWORD

In conducting the research described in this report, the investigators (s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council (DHEW Publication No. (NIA) 78-23, Revised 1978).

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## INTRODUCTION

During the Korean War more than 3,200 United Nations troops in Korea developed a rare hemorrhagic fever which attracted worldwide attention (1). Since then it has been known as Korean hemorrhagic fever (KHF). This disease is an important military problem because large epidemics have occurred among soldiers during several wars. More than 12,600 cases of epidemic hemorrhagic fever (EHF) occurred among one million Japanese soldiers in Manchuria (2) and several hundred cases occurred among Russian soldiers in the Far East (3) during World War II. Several thousand cases of war nephritis, clinically similar to Nephropatia epidemica (NE), were reported among British soldiers stationed in Flanders during World War I (4), and about 15,000 cases of NE occurred among German soldiers in Lapland and prisoners in Yugoslavia during World War II (5). About 14,000 cases of war nephritis clinically similar to NE were described among Northern Armies in the American Civil War (6). In South Korea, 500 to 900 persons are hospitalized annually with this disease and about one third of them are soldiers. There were about 14,000 cases of HFRS in China in 1986 with 7% mortality, and several hundred cases of HFRS occurred in other countries of Asia and Europe (7). The causative agent was first discovered in 1933 from Apodemus mice (8) and isolated from patients in 1976 (9). The etiologic agent of KHF has been propagated in a human cell culture line (10), and it was named hantaan virus after the hantaan river which runs along the 38th Parallel between North and South Korea (11). Antigenic, genetic properties and DNA findings indicated that hantavirus is a new genus of Hantaviridae (12,13,14,15). A close etiological relationship was established between EHF and HFRS in USSR, NE in Scandinavia and HFRS in Eastern Europe, Japan and China (9,16,17,18). The working group on HFRS at a WHO meeting in Tokyo, 1962 recommended that all above mentioned diseases with different names should be referred to as "hemorrhagic fever with renal syndrome (HFRS)" (19). Recent sero-epidemiologic surveys showed that hantaviruses are ubiquitous in the world. Antibody against hantaan virus in human sera were demonstrated in India, Thailand, Iran, Greece, U.S.S.R., Canada, Bolivia, Brazil, Gabon and Republic of Central Africa (20,21,22,23) and recently in Taiwan, Philippines, Malaysia, Singapore, Hong Kong, Fiji, Hawaii, Argentina, Uruguay and Paraguay (24). Intraspecific transmission of hantaan virus in Apodemus mice (25) was shown and infection occurred during cage-mates for up to 360 days after infection, while large amounts of virus were excreted in urine and saliva, and no evidence for the participation of ectoparasites in virus transmission was obtained. Infection with hantaan virus is thought to be silent in animals (26), but is associated with diverse clinical symptoms in man (27). A severe form is common in East Asia, while most European cases are mild. It usually produces sporadic disease, but under

specific antibody against hepatitis B virus, which is closely associated with acute hepatitis. It is also found in the serum of an urban population in some countries (13, 14). A particular laboratory test for the identification of hepatitis B virus in serum is the laboratory test for the detection of hepatitis B surface antigen (HBSAg), HBe antigen (HBeAg), and anti-HBc antibody, of which the former was fatal, occurred in 1971 (15). Research conducted in Korea and Japan using hepatitis B virus in animal rooms, 2 (Korea) and 40 (Japan) of hepatitis B virus antibodies to hepatitis B virus. Commercial rabbits bought from breeding firms in Korea and Japan were sero-positive to hepatitis B virus and serum antibodies were found in 3.5% of 791 new-born rabbits (35). We have registered a hepatitis B virus isolated from an urban rat caught in Seoul in 1970 and others in 1975 (36). Several strains of Seoul virus were isolated from urban rats caught in Korea and Japan (37). In some instances of urban and Seoul virus were isolated from blood of dogs and cats in March 1976 (38). This report indicates that hepatitis B virus and hepatitis B surface antigen are widely distributed in Korea and Japan. The results of the study indicate that infection with hepatitis B virus is a major cause of acute hepatitis B and transmission of hepatitis B virus from dogs and cats to humans may occur. It is suggested that the spread of hepatitis B virus from dogs and cats to humans should be prevented.

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mental use.

### Hantaviruses

All experimental and diagnostic work were done with Vero E-6 and A549 cells infected with Hantaan virus, serotype 10/18, Lee and Huh/9/80 isolated from patient blood and urine, and Vero E-6 cells and Seoul virus, serotype 16/39 and 82/17 isolated from Seoul and Incheon urban rats in Vero E-6 cells and Huh/82/17 isolated from a Japanese urban rat in Wistar rat cells adapted in Vero E-6 cells. To titrate the virus from rat lungs, 10% lung suspensions are prepared with BSS containing 0.2 bovine albumin clarified at 5,000 G for 20 min. at 4°C and supernatants are used as inoculum. The ID<sub>50</sub> of strains 10/18 and Lee in Apodemus mice is 10<sup>6.5</sup> and 10<sup>7.5</sup> and ID<sub>50</sub> of strains 80/39 and Huh/82/17 in Wistar rat is 10<sup>7.5</sup> and 10<sup>7.5</sup> i.u./ml, respectively. All strains of hantavirus (Seoul, Hantaan, Lee) from rodents are and proved to be identical with a potent anti-hantavirus immune sera and to be highly infectious in mice and rats after inoculation of rat lung and Seoul virus cell.

### Preparation of immune sera

In addition to conventional sera prepared from adult mice and rabbits, sera were also prepared from mice, rabbits, and guinea pigs. Details were described elsewhere (1978). From 1978, guinea pigs and rabbits and mice were employed.

### Tissue culture system

Primary and secondary Vero E-6 cells were prepared in MEM supplemented with 10% fetal calf serum (FCS) and 100 i.u./ml penicillin and 100 i.u./ml streptomycin.

### Virus inoculation

The details of intraperitoneal and intracerebral inoculation of virus are given by Lee and Vireo (1978). In brief, 100 µl of virus inoculum in Vero E-6 cells were inoculated into mice with the described procedure (1978).

Generally, 100 µl of virus inoculum were inoculated into mice intraperitoneally or intracerebrally.

The techniques employed for identification of the virus and antigens of Hantavirus in mice, rats, guinea pigs, and other animals were described elsewhere (1978). In brief, the following procedure was used for identification of the virus.

Identification of the virus in mice, rats, guinea pigs, and other animals was done by immunofluorescence and electron microscopy. Immunofluorescence was done by using anti-hantavirus serum prepared under 0.5% paraformaldehyde fixation and immunofluorescence was done by using anti-hantavirus serum prepared under 0.5% paraformaldehyde fixation. Details of the procedure for identification of the virus are given elsewhere (1978).

This test for identification of the virus in mice, rats, guinea pigs, and other animals was done by immunofluorescence and electron microscopy. Immunofluorescence was done by using anti-hantavirus serum prepared under 0.5% paraformaldehyde fixation and immunofluorescence was done by using anti-hantavirus serum prepared under 0.5% paraformaldehyde fixation. Details of the procedure for identification of the virus are given elsewhere (1978).

## RESULTS

### A. New epidemiological features of HFRS outbreaks leptospirosis and tickettsiosis during epidemic season of HFRS in Korea.

#### 1. New epidemiologic features of HFRS

There were 705 hospitalized cases of HFRS confirmed serologically at our institute in 1986 and 19 of them were 17 Army soldiers as shown in Table 1. One of the new epidemiologic features of HFRS in Korea is increasing number of HFRS patients in urban areas of Seoul as shown in Table 2. There were about 91 cases of HFRS in Seoul city in 1986. These patients were only hospitalized severe cases and usually moderate and mild cases are not included because they were usually diagnosed clinically as influenza. Patients occur throughout the year but peak is in fall in urban areas of Seoul (Table 3). HFRS cases occur in all district of Seoul as shown in Table 4. Recent findings show that there is one large epidemic peak of HFRS in the fall in Korea as shown in Table 5, and there are an increase no. of cases of HFRS among children, and male patients are dominant group of HFRS as shown in Table 6 although Army soldier patients were a minority in the no. of HFRS cases. Table 7 shows prevalence of HFRS among 204 locations in different locations and almost 70% of the patients were in Kyung-do and Jeon-do. Seasonal occurrence of HFRS were civilian, 100 Army and 1 Army as shown in Table 7.

#### 2. Epidemic outbreaks of leptospirosis and tickettsiosis during epidemic season of HFRS

As shown in Table 8, local no. of suspected cases of HFRS in 1986 is 704 among 2,065 HFRS suspected sera tested. These suspected sera were sent to our laboratory from hospitals in and nearby cities of Seoul for serologic diagnosis of HFRS but HFRS was only 349 of total patients. During epidemic season of HFRS, we have tested 1,533 sera from suspected HFRS patients for leptospirosis and confirmed 64 cases (4.2%) of leptospirosis serologically and locally incident leptospirosis was shown in Table 9. Sex of leptospirosis patients (one was soldier and 63 Army soldier patients) is shown in Tables 10 and 11. We have tested 197 sera from 197 non-leptospirosis sera against tickettsiosis and 21% of patients among these unknown patients were seropositive against tsulungarashi. There were 10 cases of HFRS patients among 197 suspected sera from 19 Army soldiers hospitalized at 17 Army hospital in Seoul and we did not find any of HFRS sera against leptospirosis and tickettsiosis and confirmed leptospirosis and one serum against as shown in Table 10. Distribution of locally leptospirosis and serum against tickettsiosis in Korea in 1986 is shown in Table 12 and name of localities the patients were occurred in Kyung-do, Seoul city and

Table 1.  
Hospitalized cases of Hemorrhagic fever with renal  
syndrome patients in the Republic of Korea

Year	US forces	Korean soldiers	Korean civilians	Total
1951	827	...	...	827
1952	833	...	...	833
1953	455	...	...	455
1954	307	...	19	326
1955	20	...	...	20
1956	23	26	...	54
1957	13	21	...	34
1958	15	20	...	35
1959	79	47	...	126
1960	10	185	...	195
1961	27	341	...	368
1962	29	311	...	340
1963	11	257	...	268
1964	22	205	...	245
1965	99	110	...	211
1966	30	82	...	122
1967	31	65	...	130
1968	25	102	...	156
1969	9	134	...	191
1970	13	221	171	375
1971	2	356	371	701
1972	0	203	166	369
1973	0	237	241	478
1974	0	291	177	427
1975	1	370	400	771
1976	4	504	...	593
1977	7	241	188	536
1978	10	168	207	385
1979	1	122	241	364
1980	1	72	177	250
1981	2	164	377	543
1982	3	123	378	504
1983	3	36	401	503
1984	3	155	569	730
1985	7	159	531	697
1986	10	166	530	706
Total	2,949	5,040	6,020	14,309

Nos. of patients since 1977 are serologically confirmed  
cases at The Institute of Viral Diseases, Korea  
University.

Table 2.  
 Number of serologically confirmed hospitalized Hemorrhagic fever with renal syndrome patients in provinces of the Republic of Korea from 1980 to 1986

Province	No. of patients							Total
	1980	1981	1982	1983	1984	1985	1986	
Seoul city	18	65	73	46	91	70	93	456
Kyunggido	82	143	146	145	240	240	252	1,248
Chungcheongdo	44	89	101	44	125	109	81	593
Kangwondo	18	67	37	128	67	62	46	425
Kyongsangdo	17	6	14	23	21	20	29	130
Chollado	6	7	7	16	24	30	29	119
Total	185	477	477	402	565	531	530	2,671



Table 3.  
 Monthly incidence of serologically confirmed Hemorrhagic fever with  
 renal syndrome patients in metropolitan areas of Seoul from 1980  
 to 1986

Year	Month												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
1980	2	0	0	1	0	1	0	1	0	1	8	4	18
1981	3	1	0	1	0	1	1	0	0	14	29	15	65
1982	6	0	4	4	1	0	2	3	5	10	22	16	73
1983	12	1	0	1	4	0	0	0	0	4	16	8	46
1984	4	3	4	6	0	3	4	1	3	15	34	15	91
1985	6	3	4	6	5	2	3	4	3	4	22	16	70
1986	4	2	2	7	6	7	8	2	7	12	15	21	93
Total	37	6	14	20	16	14	18	11	18	60	146	96	456

Table 4.  
Number of Hemorrhagic fever with renal syndrome patients in the  
district of Seoul, 1981 - 1986

Name of district	1981	1982	1983	1984	1985	1986	Total
Sungbuk-ku	5	5	2	8	3	3	26
Tobong-ku	4	6	6	7	8	4	35
Tongdaemun-ku	5	8	5	5	2	9	34
Chongro-ku	1	3	4	2	4	1	15
Chung-ku	3	2	0	3	4	3	15
Yongsan-ku	2	2	0	4	3	1	12
Mapo-ku	0	2	1	3	3	7	16
Sungdong-ku	6	12	7	6	5	12	48
Seodaemun-ku	3	1	3	3	2	4	16
Punpyung-ku	3	3	4	4	2	5	21
Kuro-ku	3	0	4	8	9	10	34
Yongdungpo-ku	9	4	0	4	2	3	22
Ewhaak-ku	6	5	2	4	5	9	31
Kangnam-ku	6	12	3	10	5	5	43
Kangdong-ku	4	5	4	6	7	4	30
Yonjizak-ku	3	0	1	6	1	2	13
Kangseo-ku	2	1	0	8	5	11	27
<b>Total</b>	<b>65</b>	<b>73</b>	<b>46</b>	<b>91</b>	<b>70</b>	<b>93</b>	<b>438</b>

Table 5.  
 Monthly incidence of Hemorrhagic fever with renal syndrome patients in the Republic of  
 Korea, 1966 - 1986

Year	Month												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
1966	2	3	3	1	4	9	6	2	1	16	56	26	129
1967	2	1	0	1	4	10	2	4	8	29	50	19	130
1968	3	1	0	4	7	9	7	6	8	40	50	21	156
1969	4	0	4	1	8	12	7	8	5	41	66	35	191
1970	1	0	0	1	6	9	8	1	15	58	154	112	365
1971	13	1	2	7	14	23	13	19	33	140	348	148	761
1972	15	5	5	12	17	27	16	10	18	80	142	42	389
1973	12	3	3	4	6	10	11	13	19	117	211	69	478
1974	11	0	1	7	17	13	13	10	19	113	151	72	427
1975	25	5	3	3	8	32	22	22	27	177	360	153	837
1976	40	12	5	11	12	36	45	33	111	156	319	112	893
1977	7	0	0	2	8	57	21	19	29	93	226	74	536
1978	17	2	2	2	11	10	11	9	9	78	156	93	406
1979	12	4	6	7	21	16	21	12	9	79	124	53	364
1980	19	6	4	3	14	11	5	9	6	40	74	63	259
1981	12	7	1	4	4	17	21	6	15	80	233	143	543
1982	44	11	10	9	15	13	16	15	15	79	178	99	504
1983	34	7	2	5	9	16	16	3	13	60	186	152	503
1984	35	7	8	10	13	24	12	10	13	125	304	169	730
1985	45	18	12	8	21	32	21	21	12	74	254	181	699
1986	46	11	3	19	22	24	24	14	25	114	213	186	706
Total	399	119	79	124	241	410	319	242	410	1,789	3,855	2,025	10,005

Table 6.  
Occurrence of HFRS patients among ROKA soldiers in different areas of Korea in 1986

Name of area	No. of patient	Name of area	No. of patient
Seoul city	1	Byukje	1
<u>Kyunggido,</u> Paju	31	Dongducheon	1
Pocheon	19	<u>Kangwondo,</u> Chuiwon	31
Kimpo	16	Inje	8
Yeoncheon	11	Whacheon	7
Yangju	7	Koseong	3
Kangwha	1	Hongcheon	2
Koyang	2	Yangju	1
Suwon	1	Whangseong	2
Kapyung	1	Samnoksok	1
Whaseong	1	Kimwha	1
Shineung	1	Kanseong	1
Ilsan	2	Sokcho	1
Songchu	1	<u>Chungcheongnamdo,</u> Nonsan	1
Incheon	1	<u>Kyungcheongnamdo,</u> Tongyoung	1
Dukjeong	2	<u>Kyungcheongbukdo,</u> Youngdong	1
Wondang	1	<u>Chullabukdo,</u> Suwon	1
Icheon	1	Seonju	1
Pyungtaek	1		

Total: 166 patients

Table 1  
 Number of serologically confirmed cases of hemorrhagic fever with renal syndrome patients at the Institute for Viral Diseases, Korea University in Korea in 1986

Year	No. of antibody positive sera against Hantaan virus			
	Civilian	ROK Army	US Army	Total
1	30/116	16/16	0/1	46/133
2	10/46	1/12	0/0	11/58
3	7/47	1/4	0/0	8/51
4	16/61	2/8	1/1	19/70
5	17/79	5/13	0/3	22/95
6	18/84	6/14	0/1	24/99
7	19/93	5/12	0/1	24/105
8	12/90	1/6	1/2	14/88
9	24/114	1/6	1/1	25/131
10	30/137	3/15	0/3	34/384
11	145/394	63/91	5/20	213/505
12	160/310	24/34	2/6	186/355
Total	536/1796	166/291	10/38	706/2074
No. of deaths	2	0	2	
Percentage		4.6%	20%	

Table 3.  
 Number of HPS, leptospirosis and scrub typhus patients diagnosed serologically among hospitalized patients at The Institute for Viral Disease, Kyoto University

	1985		1986	
Total no. of HPS	699 (19)	Total no. of HPS	705 (34%)	
Total no. of sero. tested	2,135 (67)	Total no. of sero. tested	2,068 (34%)	
Total no. of leptospirosis	435 (28)	Total no. of leptospirosis	64 (4%)	
Total no. of sero. tested	1,554 (51)	Total no. of sero. tested	1,593 (4%)	
Total no. of scrub typhus	129 (11)	Total no. of scrub typhus	215 (31%)	
Total no. of sero. tested	1,201 (41)	Total no. of sero. tested	692 (31%)	
Total no. of unknown patients	2,604 (79)	Total no. of unknown patients	948 (40%)	
Total no. of sero. tested	2,604 (79)	Total no. of sero. tested	2,068 (40%)	

Percentages in parentheses are percentages of total patients hospitalized in the respective years.

Table 1.  
 Number of confirmed hospitalized cases of HFRS, Leptospirosis and Scrub typhus among civilian at the Institute for Viral Diseases, Peking University in Korea, 1986

Month	HFRS			Leptospirosis			Scrub typhus		
	M	F	Total	M	F	Total	M	F	Total
1	24/72	6/44	30/116	14/10	4/40	18/110	n.t.	n.t.	n.t.
2	10/15	0/11	10/46	5/33	2/8	7/41	n.t.	n.t.	n.t.
3	7/34	0/13	7/47	6/34	0/12	6/46	n.t.	n.t.	n.t.
4	12/42	4/19	16/61	2/42	2/19	4/61	n.t.	n.t.	n.t.
5	14/51	3/19	17/79	3/48	1/17	4/65	n.t.	n.t.	n.t.
6	13/60	5/25	18/85	0/43	0/17	0/60	n.t.	n.t.	n.t.
7	16/68	3/21	19/89	1/61	0/18	1/79	n.t.	n.t.	n.t.
8	8/52	4/23	12/75	1/25	0/13	1/39	n.t.	n.t.	n.t.
9	15/63	5/30	20/93	6/31	2/30	8/114	n.t.	n.t.	n.t.
10	43/155	22/103	76/258	5/112	2/151	7/256	25/12	48/92	73/114
11	101/224	44/170	145/394	2/204	0/160	2/364	32/95	48/142	80/237
12	119/216	41/103	160/319	0/27	0/25	0/52	5/135	12/112	17/247
Total	389/1107 (24.8%)	144/647 (22.3%)	530/1755 (30.2%)	45/814 (5.5%)	13/513 (2.5%)	58/1327 (4.4%)	62/292 (28.1%)	108/346 (31.2%)	170/638 (26.6%)

∇ : No. of serologically confirmed patient  
 No. of suspected patient tested

Table 14. - Reported hospitalized cases of HUS, Leptospirosis and Scrub Typhus  
 from all patients at the National Children's Hospital, Kyoto University in Period  
 1957

Year	HUS	Leptospirosis	Scrub Typhus
1957	116	116	n.t.
1958	111	112	n.t.
1959	111	114	n.t.
1960	116	116	n.t.
1961	111	111	n.t.
1962	111	116	n.t.
1963	111	116	n.t.
1964	111	116	n.t.
1965	111	116	n.t.
1966	111	116	n.t.
1967	111	116	n.t.
1968	111	116	n.t.
1969	111	116	n.t.
1970	111	116	n.t.
1971	111	116	n.t.
1972	111	116	n.t.
1973	111	116	n.t.
1974	111	116	n.t.
1975	111	116	n.t.
1976	111	116	n.t.
1977	111	116	n.t.
1978	111	116	n.t.
1979	111	116	n.t.
1980	111	116	n.t.
1981	111	116	n.t.
1982	111	116	n.t.
1983	111	116	n.t.
1984	111	116	n.t.
1985	111	116	n.t.
1986	111	116	n.t.
1987	111	116	n.t.
1988	111	116	n.t.
1989	111	116	n.t.
1990	111	116	n.t.
1991	111	116	n.t.
1992	111	116	n.t.
1993	111	116	n.t.
1994	111	116	n.t.
1995	111	116	n.t.
1996	111	116	n.t.
1997	111	116	n.t.
1998	111	116	n.t.
1999	111	116	n.t.
2000	111	116	n.t.
2001	111	116	n.t.
2002	111	116	n.t.
2003	111	116	n.t.
2004	111	116	n.t.
2005	111	116	n.t.
2006	111	116	n.t.
2007	111	116	n.t.
2008	111	116	n.t.
2009	111	116	n.t.
2010	111	116	n.t.
2011	111	116	n.t.
2012	111	116	n.t.
2013	111	116	n.t.
2014	111	116	n.t.
2015	111	116	n.t.
2016	111	116	n.t.
2017	111	116	n.t.
2018	111	116	n.t.
2019	111	116	n.t.
2020	111	116	n.t.
2021	111	116	n.t.
2022	111	116	n.t.
2023	111	116	n.t.
2024	111	116	n.t.
2025	111	116	n.t.
2026	111	116	n.t.
2027	111	116	n.t.
2028	111	116	n.t.
2029	111	116	n.t.
2030	111	116	n.t.
2031	111	116	n.t.
2032	111	116	n.t.
2033	111	116	n.t.
2034	111	116	n.t.
2035	111	116	n.t.
2036	111	116	n.t.
2037	111	116	n.t.
2038	111	116	n.t.
2039	111	116	n.t.
2040	111	116	n.t.
2041	111	116	n.t.
2042	111	116	n.t.
2043	111	116	n.t.
2044	111	116	n.t.
2045	111	116	n.t.
2046	111	116	n.t.
2047	111	116	n.t.
2048	111	116	n.t.
2049	111	116	n.t.
2050	111	116	n.t.
2051	111	116	n.t.
2052	111	116	n.t.
2053	111	116	n.t.
2054	111	116	n.t.
2055	111	116	n.t.
2056	111	116	n.t.
2057	111	116	n.t.
2058	111	116	n.t.
2059	111	116	n.t.
2060	111	116	n.t.
2061	111	116	n.t.
2062	111	116	n.t.
2063	111	116	n.t.
2064	111	116	n.t.
2065	111	116	n.t.
2066	111	116	n.t.
2067	111	116	n.t.
2068	111	116	n.t.
2069	111	116	n.t.
2070	111	116	n.t.
2071	111	116	n.t.
2072	111	116	n.t.
2073	111	116	n.t.
2074	111	116	n.t.
2075	111	116	n.t.
2076	111	116	n.t.
2077	111	116	n.t.
2078	111	116	n.t.
2079	111	116	n.t.
2080	111	116	n.t.
2081	111	116	n.t.
2082	111	116	n.t.
2083	111	116	n.t.
2084	111	116	n.t.
2085	111	116	n.t.
2086	111	116	n.t.
2087	111	116	n.t.
2088	111	116	n.t.
2089	111	116	n.t.
2090	111	116	n.t.
2091	111	116	n.t.
2092	111	116	n.t.
2093	111	116	n.t.
2094	111	116	n.t.
2095	111	116	n.t.
2096	111	116	n.t.
2097	111	116	n.t.
2098	111	116	n.t.
2099	111	116	n.t.
2100	111	116	n.t.

V. ...



Table 11.  
 Number of confirmed hospitalized cases of HFRS, Leptospirosis and Scrub typhus among US Army soldiers at The Institute for Viral Diseases, Korea University in Korea, 1986

Month	HFRS	Leptospirosis	Scrub typhus
1	0/1 <sup>✓</sup>	1/1	n.t.
2	0/0	0/0	n.t.
3	0/0	0/0	n.t.
4	1/0	0/1	n.t.
5	0/3	0/3	n.t.
6	0/1	0/1	n.t.
7	0/0	0/0	n.t.
8	1/2	0/2	n.t.
9	1/1	0/1	n.t.
10	0/3	0/4	n.t.
11	5/20	0/20	1/1
12	2/6	n.t.	n.t.
Total	10/38 (26.3%)	1/32 (3.1%)	1/1

✓ : No. of serologically confirmed patient  
 No. of suspected patient tested

Table 12.  
Distribution of confirmed cases of HFRS, Leptospirosis and Scrub typhus  
in Korea in 1986 at The Institute for Viral Diseases, Korea University

Name of Province	HFRS	Leptospirosis	Scrub typhus
Seoul city	93	16	15
Incheon city	14	2	0
Pusan city	5	1	1
Kyunggi-do	238	20	92
Kangwon-do	46	3	15
Chungcheongbuk-do	27	4	18
Chungcheongnam-do	54	5	15
Jeollabuk-do	24	5	9
Jeollanam-do	3	1	5
Kyongsangbuk-do	14	1	0
Kyongsangnam-do	9	0	0
Total	510	58	170

Table 1. Distribution of H1N1, Influenza virus and other typhus in Korea, 1986

Age	H1N1			Influenza virus			Scrub typhus		
	M	F	Total (%)	M	F	Total (%)	M	F	Total (%)
0-10	3	0	3(1.6)	0	0	0	1	1	1(0.6)
1-10	20	8	28(14.4)	2	0	2(3.4)	1	1	2(1.2)
2-20	40	21	61(29.7)	5	0	5(8.6)	4	11	15(8.8)
3-30	11	13	24(11.8)	6	2	11(19.0)	9	5	14(8.2)
4-50	12	23	35(16.9)	7	5	12(20.7)	13	19	32(19.4)
50-70	20	32	52(25.0)	14	2	16(27.6)	13	36	49(29.3)
Total	119	107	226(111.2)	54	4	12(21.4)	67	109	176(100)
									(6.5)(63.5)

Chuncheon-do. It is noteworthy that about 50% of scrub typhus patients was female and 60% of the patients were in the group of 40-50, but about 75% of leptospirosis patients was male in age group of 50-60 as shown in Table 13.

3. Seroepidemiology survey of wild and house rodents with Hantavirus, Leptospira and R. tsutsugamushi in Korea, 1986.

It is known that Hantaan and Seoul viruses in the Genus Hantavirus, Leptospira interrogans, and R. tsutsugamushi are the causative agents of HFRS, leptospirosis and scrub typhus in Korea. We have carried out a seroepidemiologic survey of wild rodents against these agents since rodents are the reservoir hosts for all of these agents. Apodemus mice, Mus musculus mice and shrews were captured in the endemic areas of HFRS in the summer and fall of 1986. Urban house rats were captured in 7 harbor cities along the coast of South Korea and in Wonju, an endemic area of HFRS from June to December 1986. As shown in Table 14, 14% of 230 Apodemus mice and 30% of 197 house rats were seropositive against Hantavirus, 9% of 211 Apodemus mice, 3 out of 8 Microtus mice, and 21% of 115 house rats were seropositive against Leptospira interrogans. Sixty-eight of 190 Apodemus mice, 3 out of 20 Microtus mice, and 5 of 139 house rats were seropositive against R. tsutsugamushi. The infection rate of Apodemus mice and house rats with Hantavirus in Korea is almost the same as found previously, but the high infection rate of field mice and house rats with Leptospira and Rickettsia is not unlike. Table 15, 16, and 17 show the rate of rodents of various infections with Hantavirus, R. tsutsugamushi and Leptospira in wild rodents. Apodemus mice, Microtus mice, and house rats and some of Microtus mice were proved to be infected with two or three agents based upon the agglutination of the antibodies at the same time. It can be concluded that there will be more cases of HFRS in urban areas and more cases of leptospirosis and scrub typhus in rural areas in the next years in Korea, because of high infection rate of rodents caused by Hantavirus, and increasing population of rodents in urban areas.

Table 14.  
Epidemiologic survey of infected rodents with hantavirus, leptospirosis and  
brucellosis in Korea, 1966

No. of animal	Location	Date	No. of infected animal		
			Hantavirus	Leptospirosis	Brucellosis
1	Kunnamyeon, Yeonchungkun,	23 - 25 June	2/34	0/34	n.t.
	"	27 - 31 Oct.	6/57	6/57	42/57
	"	3 - 6 Nov.	4/46	5/46	34/46
	Chuksungmyeon, Pajukun,	17 - 21 Nov.	14/41	6/45	27/45
2	Wuncheonmyeon, Pochunkun	9 - 14 Dec.	3/46	5/46	30/46
Total			31/224 (13.8%)	21/230 (9.1%)	135/196 (68.9%)
3	Kunnamyeon, Yeonchungkun,	27 - 31 Oct.	4/6	2/6	5/6
		3 - 6 Nov.	1/2	1/2	2/2
Total			5/8	3/8	7/8 (87.5%)
4	Chuksungmyeon, Pajukun,	17 - 21 Nov.	5/6	6/6	6/6
		Wuncheonmyeon, Pochunkun	9 - 14 Dec.	3/6	5/6
Total			8/12	11/12	11/12
5	Samchuk city	9 - 14 June	10/11	n.t.	n.t.
	Zusan city	21 - 25 July	4/11	3/11	7/11
	Bisan city	16 - 22 Aug.	5/26	4/26	6/26
	Busan city	1 - 5 Sept.	11/21	11/26	11/26
	Sokcho city	22 - 27 Sept.	6/14	4/14	9/14
	Mokpo city	10 - 14 Nov.	13/15	6/16	2/16
	Yeosu city	24 - 28 Nov.	7/11	6/19	6/19
	Wuncheonmyeon, Pochunkun,	9 - 14 Dec.	6/11	9/31	6/31
	Total			48/101 (47.5%)	43/136 (31.6%)

Table 15.  
Antibody test of *Apodemus agrarius* against Hantavirus, *Rickettsia tsutsugamushi* and *Leptospira interrogans* caught in endemic areas of HFRS in Korea, 1986

Location	Date of collection	No. of antibody positive/no. of mice tested					
		HIV	RV	IV	H+R	H+I	R+L H+R+L
Yeoncheon	June '86	2/34	n.t.	0/34	n.t.	n.t.	n.t.
Yeoncheon	Oct. '86	9/57	42/57	8/57	2/57	0/57	3/57
Yeoncheon	Nov. '86	6/48	34/48	5/48	4/48	0/48	5/48
Paju	Nov. '86	14/45	21/45	5/45	10/45	0/45	1/45
Wancheon	Dec. '86	0/16	30/46	3/46	0/46	0/46	1/46
Total		31/236 (13%)	153/153 (100%)	21/236 (9%)	16/196 (8%)	0/196 (0%)	16/196 (8%)

HIV : Hantavirus IgG (HFRS)  
 RV : *Rickettsia tsutsugamushi* IgG (HFRS)  
 IV : *Leptospira interrogans* IgG (HFRS)

Table 16.

Antibody test of wild urban rats against Hantavirus, Rickettsia tsutsugamushi and Leptospira interrogans caught in different areas of Korea, 1986

Location	Date of collection	No. of antibody positive/no. of rats tested						
		HV	RV	LV	R+R	R+L	R+L	H+R+L
Samcheok	June '86	10/18	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
Kunsan	July '86	2/11	0/11	1/11	0/11	0/11	0/11	0/11
Ulsan	Aug. '86	7/20	0/20	5/20	0/20	3/20	0/20	0/20
Sokcho	Sept. '86	3/14	0/14	0/14	0/14	2/14	0/14	0/14
Pusan	Sept. '86	11/26	0/26	12/26	0/26	5/26	0/26	0/26
Mokpo	Nov. '86	2/18	2/18	0/18	1/18	0/18	0/18	0/18
Yeosu	Nov. '86	7/19	0/19	0/19	0/19	0/19	0/19	0/19
Wunchun	Dec. '86	5/31	5/31	5/31	2/31	0/31	1/31	1/31
Total		47/157 (30%)	7/139 (5%)	19/139 (14%)	1/139 (0%)	10/139 (7%)	1/139 (1%)	1/139 (1%)

- ✓ : Hantavirus 7/139 (5%)  
 ✓ : Rickettsia tsutsugamushi 1/139 (0%)  
 ✓ : Leptospira interrogans 1/139 (1%)

Table 17.

Antibody test of wild urban rats against Hantavirus, Rickettsia tsutsugamushi and Leptospira interrogans caught in endemic areas of HPRS in Korea, 1986

Location	Date of collection	No. of antibody positive/no. of rats tested						
		HV	RV	LV	R+R	R+L	R+L	H+R+L
Yeoncheon	Oct. '86	0/6	1/6	1/6	0/6	0/6	1/6	0/6
Yeoncheon	Nov. '86	0/2	1/2	1/2	0/2	0/2	1/2	0/2
Total		0/8	2/8 (25%)	2/8 (25%)	0/8	0/8	2/8 (25%)	0/8

- ✓ : Hantavirus 7/139 (5%)  
 ✓ : Rickettsia tsutsugamushi 1/139 (0%)  
 ✓ : Leptospira interrogans 1/139 (1%)

B. Global serologic surveys for the hantavirus infection.

As WHO Collaborating Centre for Research on Haemorrhagic fever with renal syndrome (HFRS), we have been providing serological diagnosis for suspect HFRS in sera from throughout the world, but especially from the Asian region. In addition, we are collaborating with a number of investigators conducting small mammal surveys for evidence of hantavirus infection and isolation of virus from host animal tissues. Results of these preliminary studies indicate that human disease due to hantavirus infection is present in several areas where HFRS had not been previously diagnosed. The results of the serosurvey of hantaviruses among rats and human populations in many parts of the world where HFRS patients are not known to exist are shown in Table 16.

Human sera from 17 countries; 5 countries in Pacific Ocean, 1 country in North America, 4 countries in South American and 3 countries in Africa were found to have IF antibodies to hantaan virus as shown in Table 18. The prevalence rate of antibodies to hantaan virus was between 1.1% - 13.0%, data much higher than those of residents of Seoul, the endemic area of HFRS. Very recently, we have confirmed HFRS patients serologically among hospitalized patients in Hong Kong, Taiwan, Malaysia and Sri Lanka.

Urban rat sera from the Philippines, Hong Kong, Malaysia, Singapore, Fiji, Hawaii, Chile, Sudan and Uganda were also found to have IF antibody to hantaan virus with a high prevalence rate of 61.5% among Philippine rats and 20.0% in Egypt rats.

Laboratory-bred white mice from Malaysia, Hong Kong, Singapore, Hawaii and Argentina were also positive against hantaan virus. Five out of 11 *Calomys* mice from Egypt and 4 out of 30 *Calomys* mice from Argentina were also positive to hantaan virus. Clearly the hantavirus is a near global distribution and adapted to a variety of different ecological settings. The areas to which hantaviruses cause human disease, especially in areas where HFRS has not been traditionally recognized, is presently unknown.



Table 18.  
Seroepidemiologic survey of Hantavirus infection among human and rodent in some parts of the world where HFRS is not known to exist from 1981 to 1987 at WHO Collaborating Centre for Virus Reference and Research (HFRS), Seoul

Country	No. of IF antibody positive to Hantaan virus/No. tested		
	Human	Urban rats	Laboratory rats
Hong Kong	16/322 $\checkmark$ (5.0%)	26/140 $\checkmark$ (18.6%)	3/62 (4.8%)
Philippines	20/400 (5.0%)	86/167 (51.5%)	
Malaysia	3/329 (1.0%)	10/204 (4.9%)	12/154 (27.3%)
Singapore	2/21 $\checkmark$ (9.5%)	6/52 (11.5%)	5/38 (13.2%)
Taiwan	31/240 $\checkmark$ (13.0%)		
India	1/89 (1.1%)		
Sci Lanka	14/155 $\checkmark$ (9.0%)	13/117 $\checkmark$ (11.1%)	
Fiji	3/145 (5.5%)	7/54 (6.1%)	0/3
Hawaii	15/232 (6.5%)	14/177 $\checkmark$ (8.0%)	5/59 (7.2%)
Egypt	5/453 (1.3%)	133/2,753 $\checkmark$ (29.0%)	5/71 (7.0%)
Sudan		23/452 (8.0%)	
Uganda	15/335 (4.5%)	3/54 (4.7%)	
Brazil	31/530 (7.4%)		
Argentina	15/309 (5.2%)	9/31	11/102 (13.7%)
Uruguay	4/205 (1.0%)		
Bolivia	7/23 (7.1%)		
Canada	2/2,063 (1.4%)		

$\checkmark$  : 4 HFRS patients  
 $\checkmark$  : 1 HFRS patient  
 $\checkmark$  : 2 HFRS patients  
 $\checkmark$  : 1 HFRS patient and died  
 $\checkmark$  : Isolated Seoul virus-like virus  
 $\checkmark$  : Isolated Seoul virus-like virus  
 $\checkmark$  : Isolated Seoul virus-like virus

### C. Seoul virus infection

Urban cases of HFRS in Korea, Japan, and Southeast Asia, and laboratory infections in Korea and Japan are caused by Seoul virus (31,41-43). Urban commensal rats (Rattus norvegicus and Rattus rattus) and laboratory rats are main reservoir hosts and transmit the disease to man. While some urban and laboratory infections are severe, many are milder than Hantaan virus infection. In general, the phases of disease are shorter than in classic KH<sub>1</sub>F, and sometimes it is difficult to recognize distinct phases. The clinical manifestations of the disease include high fever, fatigue, anorexia, vomiting, backache, myalgia, abdominal pain, conjunctival injection, petechiae on the soft palate, and hepatomegaly. Laboratory abnormalities include proteinuria, microscopic hematuria, lymphocytosis, thrombocytopenia, increased serum transaminases and transient glucosuria. The findings are based on observation of 56 cases of Seoul virus infection in Korea and Japan. The most characteristic manifestations of this infection are prominent abdominal symptoms, hepatomegaly and hepatic dysfunction, and mild renal dysfunction. Comparison of the clinical features of HFRS caused by different serotypes of Hantavirus are shown in Table 19.

Recently we have documented three cases of HFRS in Hong Kong, one case in Sri Lanka and two cases of HFRS in Malaysia, tropical areas where the disease was not known to exist. Serologic confirmation of the diagnosis of HFRS was obtained by the demonstration of a significant increase in antibody titer to Seoul virus in the patients' acute and convalescent phase sera.

The clinical findings in all six patients, who were diagnosed as having hepatitis, included fever, chills, jaundice, thrombocytopenia, microhematuria, and abnormal liver and renal function. Renal involvement, which is characteristic of HFRS, was mild. A prominent finding was marked elevation of serum transaminases successive of hepatitis. Severe thrombocytopenia was associated with a petechial eruption. The 2 Malaysia patients with HFRS were diagnosed as dengue in one case and leptospirosis in the other. The clinical features in these patients were not typical of HFRS.

Table 19.  
Comparison of clinical features of HFRS in countries of Euro-Asia

Clinical and laboratory findings	Infection with different serotype of Hantavirus			
	Hantaan virus		Seoul virus	Puumala virus
	Korea <sup>1</sup>	China <sup>2</sup>	Japan & Korea <sup>3</sup>	Finland <sup>4</sup>
Fever	100%	100%	100%	100%
Anorexia	-	-	70	70
Chills	92	-	50	60
Nausea	82	72	-	70
Vomiting	83	58	41	75
Backache	55	-	27	22
Myalgia	78	69	51	20
Headache	88	83	41	60
Abdominal pain	28	28	27	33
Constipation	38	-	21	28
Diarrhea	11	11	23	11
Dizziness and Vertigo	100	41	77	100
Ophthalmalgia	-	38	19	10
Blurred vision	-	18	-	10
Conjunctival injection	64	28	73	71
Pharyngeal or palatal injection	55	64	79	70
Petechiae on body	32	38	19	10
Hemorrhages (hematemesis, epistaxis, melena, etc.)	72	51	23	10
Hepatomegaly	8	-	19	10
Splenomegaly	1	-	19	10
Lymphadenopathy	36	-	19	10
Preorbital edema	8	11	19	10
Proteinuria	68	-	19	100
Hematuria	85	38	19	100
Oliguria $\leq 500$ ml	67	41	19	100
Polyuria $> 2000$ ml	91	11	19	100
Leukocytosis $> 10000/\text{mm}^3$	91	11	19	100
Thrombocytopenia $< 100000/\text{mm}^3$	72	78	19	100
Increased ESR $> 20\text{mm}/\text{h}$	72	-	19	100
BUN $> 20$ or Crtn $> 2$ mg/dl	94	11	19	100
Hypotension ( $< 90/60$ mmHg)	88	41	19	100

- <sup>1</sup> : Counts and Seltzer, 48 cases (1974)
- <sup>2</sup> : Cohen, et al. 71 cases (1981)
- <sup>3</sup> : Morimoto, et al. 27 cases (1969)
- <sup>4</sup> : Iähddevirta, 76 cases (1971)

D. Abortion of a fetus due to vertical transmission of Hantaan virus in a pregnant woman

Recently we documented vertical transmission of Hantaan virus in a 28 year old pregnant woman, who was admitted to hospital in her 8th month of pregnancy. She suffered from classical HFRS caused by Hantaan virus infection. During the convalescent phase of illness (hospital day 26), she developed uterine bleeding and subsequently delivered a 3.3 Kg fetus which died 11 hours after birth. Autopsy revealed variable degrees of hemorrhage in the kidneys, heart, lungs, and adrenal glands similar to the pathologic findings in adults with fatal HFRS (44).

The IgG immunofluorescent antibody titer to Hantaan virus in maternal blood was 4,096 and the IgM titer 256. In fetal blood sampled from the umbilical cord, the IgG antibody titer was 8,192 and the IgM titer 256. The clinical course of the patient is shown in Figures 1 and 2. This is the first report of vertical transmission of Hantaan virus from mother to child confirmed by serologic and pathologic findings. Details of the autopsy findings on the fetus are following. Autopsy findings on fetus infected in utero with Hantaan virus.

Lungs: The right and left lungs showed slight thickening of alveolar septa. The alveolar spaces were lined by cuboidal cells. Amorphous or band-like eosinophilic material was noted on the alveolar surface in some alveoli. Bronchioles were unremarkable. Vascular congestion was evident with slight hemorrhage in enveloping connective tissue.

Heart: There was mild interstitial edema, congestion, and hemorrhage in the myocardium. Coronary arteries were unremarkable.

Stomach: The epithelium was well preserved. The lamina propria showed mild diffuse vascular congestion and hemorrhage and infiltration with small numbers of lymphocytes. The muscularis and serosa were unremarkable.

Liver: The lobular architecture was well preserved. Large numbers of hematopoietic cells were noted in the sinusoidal spaces. The hepatocytes and bile ducts were unremarkable.

Adrenals: There was diffuse cortical hemorrhage and severe thickening of the cortical layer. The cortical cells exhibited swollen eosinophilic cytoplasm. There was no hematopoiesis.

Kidneys: Renal cortical and medullary architecture was well formed. There was interstitial hemorrhage in the medullary region.

Spleen: The capsule was thin. The white pulp was well preserved. The medullary spaces were markedly congested with evidence of focal hemorrhage and extramedullary hematopoiesis.

Placenta and umbilical cord: Multifocal areas of hemorrhage were present.

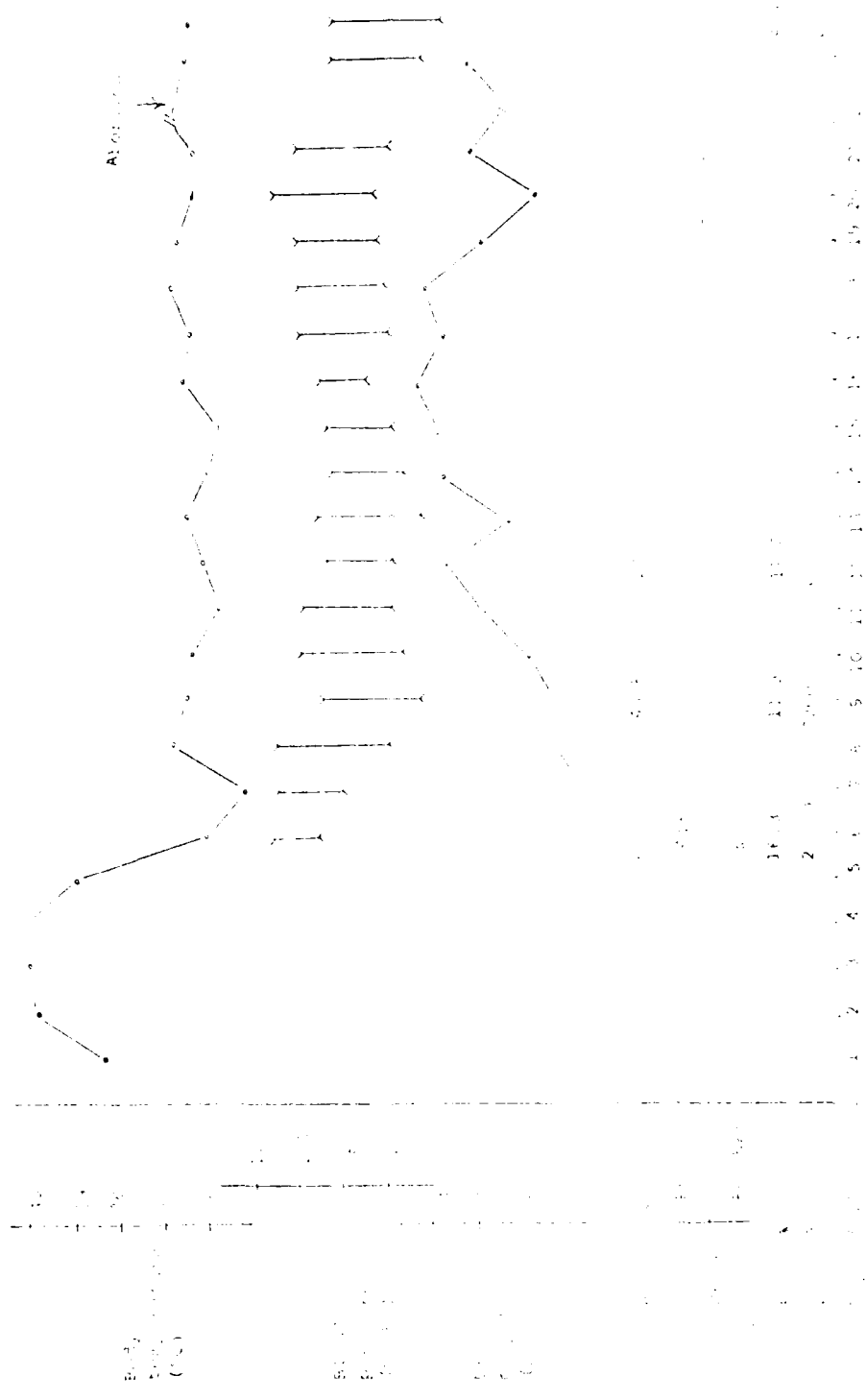


Fig. 1. Schematic diagram of the structure of the Algol system with the main parameters.

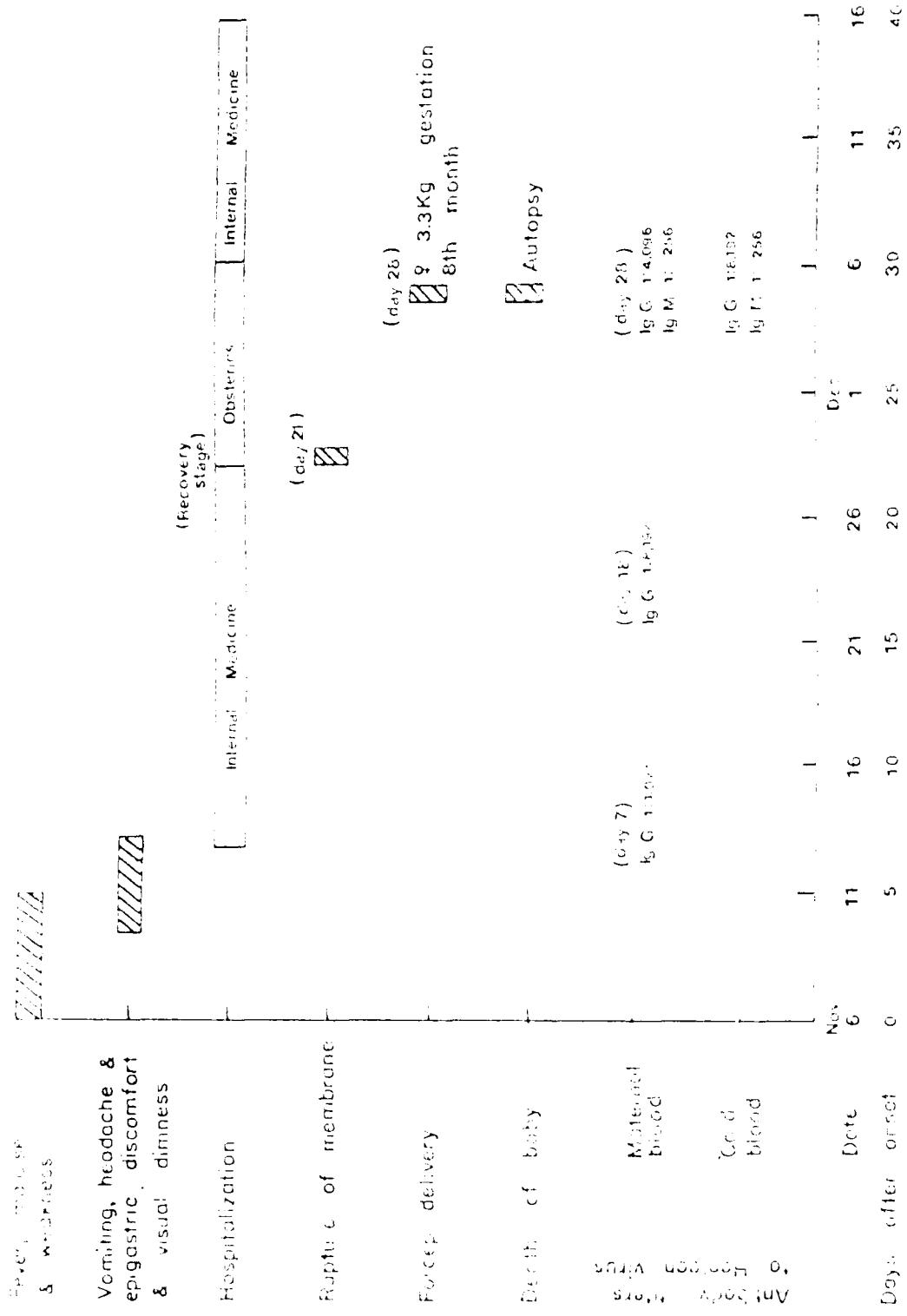


Fig. 2. Vertical transmission of Hantaan virus in a pregnant woman (28 years, 8th month of pregnancy)

E. Comparative sensitivity of assays for diagnosis of HFRS and the efficacy of immunoprecipitation.

The available serologic assays for HFRS are indirect IF antibody technique (IFAT), solid phase antibody assay, IAHA test and plaque reduction neutralization test (PRNT). IFAT and Elisa are very sensitive and rapid. Indirect antibody test, IAHA test and PRNT are specific for viral serotypes but time-consuming. The most widely employed routine diagnostic tests for HFRS are IFAT and ELISA and demonstration of IgM antibodies against Hantavirus in sera from suspect patients is pathognomonic for HFRS.

As shown in Table 20, IgG antibodies to Hantaan virus were demonstrated in sera from 7 past HFRS patients but no IgM antibodies were detected. All Hantaan antibodies were 5-50 times higher than Ig and neutralizing antibody titers. IF, ELISA and PRNT antibodies persisted for at least 1 to 17 years after illness. PRNT is sensitive and specific for the infecting serotype virus. This was confirmed since 5 of the 7 past HFRS patients were infected with Hantaan virus and 2 with Seoul virus. These patients had no titers of IF antibodies but high titers of ELISA and PRNT antibodies against the infecting virus. As one of the most sensitive serologic tests, the ELISA can be used for seroepidemiology surveys, while the specificity of PRNT makes it useful for serotyping of hantaviruses.

It is not yet clear whether non-specific IF antibodies against Hantaan virus exist in human and animal sera. We have tested 13 sera from healthy rats that contained IF antibodies (titers between 10-50) reacting with Hantaan and Seoul viruses, and showed no cross-reactivity with Seoul virus. The results were negative with other techniques as shown in Table 21. This suggests that there are either non-specific IF antibodies in rat sera against Hantaan or Seoul viruses, or unknown HFRS related hantaviruses that produce cross reacting IF antibodies.

At present, the interpretation of low titer IF antibodies in humans is problematic. Studies of human sera containing low titer IF antibodies employing ELISA and PRNT are in progress to determine if similar results will be found in man.

Table 20.  
Comparative titration of antibodies against Hantavirus and Seoul virus of sera from  
100 blood donors of the staff of the Institute for Viral Diseases, Korea University  
by different serologic diagnostic tests.

Sex	Years after infection	IFA test		ELISA test		PCR		Infection history
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	
FD, S.A.	17	26	12000	0	400	60	60	field visit
FD, S.W.	10	148	12000	0	1000	80	80	work place
FD, I.D.	8	32	600	0	200	16	16	work place
FD, S.A.	7	28	12000	0	100	6	6	field visit
FD, S.A.	6	16	12000	0	40	4	4	field visit
FD, S.A.	5	16	12000	0	20	2	2	field visit
FD, S.A.	4	16	12000	0	20	2	2	field visit
FD, S.A.	3	16	12000	0	20	2	2	field visit
FD, S.A.	2	16	12000	0	20	2	2	field visit
FD, S.A.	1	16	12000	0	20	2	2	field visit

FD, field visit; S.A., Seoul virus; S.W., Seoul virus; I.D., infection date.



2000 1000 500 250 100 50 25 10 5 2.5 1.25 .625 .3125

2000 1000 500 250 100 50 25 10 5 2.5 1.25 .625 .3125

Year	1890	1900	1910	1920	1930	1940	1950	1960	1970	1980	1990	2000
Population	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000
Area	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000
Volume	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000
Weight	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000
Length	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000
Width	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000
Height	1000	1500	2000	2500	3000	4000	5000	6000	7000	8000	9000	10000

Estimated population for 2000 is 10,000  
Estimated area for 2000 is 10,000  
Estimated volume for 2000 is 10,000  
Estimated weight for 2000 is 10,000  
Estimated length for 2000 is 10,000  
Estimated width for 2000 is 10,000  
Estimated height for 2000 is 10,000

THE EFFECTS OF THE 1918-1919 PANDEMIC INFLUENZA IN THE  
UNITED STATES

The 1918-1919 pandemic influenza, often referred to as the "Spanish Flu," was one of the most devastating influenza pandemics in human history. It is estimated that it caused between 40 million and 100 million deaths worldwide. In the United States, the pandemic was particularly severe, with an estimated 675,000 deaths. The virus was highly virulent, and it is believed to have been caused by a reassortment of genetic material from different influenza viruses, possibly in a bird or pig host. The pandemic was characterized by a double-peak pattern, with a first wave in 1918 and a second, less severe wave in 1919. The 1918 wave was particularly deadly, with a high mortality rate among young adults, which is unusual for influenza. The pandemic also had significant social and economic impacts, including the closure of schools and businesses, and the implementation of public health measures such as mask-wearing and social distancing. The study of the 1918-1919 pandemic has provided valuable insights into the evolution of influenza viruses and the potential for future pandemics.

Table 29.  
 Cumulative mortality of samples 1 and 11 with respect to avian virus  
 in India for 30 days after the onset of infection in Singapore.

Age and sex	Number of birds	Number of birds dying	Percentage mortality	Net survivors
Female, 10 days	10	1	10	9
Female, 12 days	10	1	10	9
Female, 14 days	10	1	10	9
Female, 16 days	10	1	10	9
Female, 18 days	10	1	10	9
Female, 20 days	10	1	10	9
Female, 22 days	10	1	10	9
Female, 24 days	10	1	10	9
Female, 26 days	10	1	10	9
Female, 28 days	10	1	10	9
Female, 30 days	10	1	10	9
Female, 32 days	10	1	10	9
Female, 34 days	10	1	10	9
Female, 36 days	10	1	10	9
Female, 38 days	10	1	10	9
Female, 40 days	10	1	10	9
Female, 42 days	10	1	10	9
Female, 44 days	10	1	10	9
Female, 46 days	10	1	10	9
Female, 48 days	10	1	10	9
Female, 50 days	10	1	10	9
Female, 52 days	10	1	10	9
Female, 54 days	10	1	10	9
Female, 56 days	10	1	10	9
Female, 58 days	10	1	10	9
Female, 60 days	10	1	10	9
Female, 62 days	10	1	10	9
Female, 64 days	10	1	10	9
Female, 66 days	10	1	10	9
Female, 68 days	10	1	10	9
Female, 70 days	10	1	10	9
Female, 72 days	10	1	10	9
Female, 74 days	10	1	10	9
Female, 76 days	10	1	10	9
Female, 78 days	10	1	10	9
Female, 80 days	10	1	10	9
Female, 82 days	10	1	10	9
Female, 84 days	10	1	10	9
Female, 86 days	10	1	10	9
Female, 88 days	10	1	10	9
Female, 90 days	10	1	10	9
Female, 92 days	10	1	10	9
Female, 94 days	10	1	10	9
Female, 96 days	10	1	10	9
Female, 98 days	10	1	10	9
Female, 100 days	10	1	10	9
Female, 102 days	10	1	10	9
Female, 104 days	10	1	10	9
Female, 106 days	10	1	10	9
Female, 108 days	10	1	10	9
Female, 110 days	10	1	10	9
Female, 112 days	10	1	10	9
Female, 114 days	10	1	10	9
Female, 116 days	10	1	10	9
Female, 118 days	10	1	10	9
Female, 120 days	10	1	10	9
Female, 122 days	10	1	10	9
Female, 124 days	10	1	10	9
Female, 126 days	10	1	10	9
Female, 128 days	10	1	10	9
Female, 130 days	10	1	10	9
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Female, 134 days	10	1	10	9
Female, 136 days	10	1	10	9
Female, 138 days	10	1	10	9
Female, 140 days	10	1	10	9
Female, 142 days	10	1	10	9
Female, 144 days	10	1	10	9
Female, 146 days	10	1	10	9
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Female, 150 days	10	1	10	9
Female, 152 days	10	1	10	9
Female, 154 days	10	1	10	9
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Female, 160 days	10	1	10	9
Female, 162 days	10	1	10	9
Female, 164 days	10	1	10	9
Female, 166 days	10	1	10	9
Female, 168 days	10	1	10	9
Female, 170 days	10	1	10	9
Female, 172 days	10	1	10	9
Female, 174 days	10	1	10	9
Female, 176 days	10	1	10	9
Female, 178 days	10	1	10	9
Female, 180 days	10	1	10	9
Female, 182 days	10	1	10	9
Female, 184 days	10	1	10	9
Female, 186 days	10	1	10	9
Female, 188 days	10	1	10	9
Female, 190 days	10	1	10	9
Female, 192 days	10	1	10	9
Female, 194 days	10	1	10	9
Female, 196 days	10	1	10	9
Female, 198 days	10	1	10	9
Female, 200 days	10	1	10	9
Female, 202 days	10	1	10	9
Female, 204 days	10	1	10	9
Female, 206 days	10	1	10	9
Female, 208 days	10	1	10	9
Female, 210 days	10	1	10	9
Female, 212 days	10	1	10	9
Female, 214 days	10	1	10	9
Female, 216 days	10	1	10	9
Female, 218 days	10	1	10	9
Female, 220 days	10	1	10	9
Female, 222 days	10	1	10	9
Female, 224 days	10	1	10	9
Female, 226 days	10	1	10	9
Female, 228 days	10	1	10	9
Female, 230 days	10	1	10	9
Female, 232 days	10	1	10	9
Female, 234 days	10	1	10	9
Female, 236 days	10	1	10	9
Female, 238 days	10	1	10	9
Female, 240 days	10	1	10	9
Female, 242 days	10	1	10	9
Female, 244 days	10	1	10	9
Female, 246 days	10	1	10	9
Female, 248 days	10	1	10	9
Female, 250 days	10	1	10	9
Female, 252 days	10	1	10	9
Female, 254 days	10	1	10	9
Female, 256 days	10	1	10	9
Female, 258 days	10	1	10	9
Female, 260 days	10	1	10	9
Female, 262 days	10	1	10	9
Female, 264 days	10	1	10	9
Female, 266 days	10	1	10	9
Female, 268 days	10	1	10	9
Female, 270 days	10	1	10	9
Female, 272 days	10	1	10	9
Female, 274 days	10	1	10	9
Female, 276 days	10	1	10	9
Female, 278 days	10	1	10	9
Female, 280 days	10	1	10	9
Female, 282 days	10	1	10	9
Female, 284 days	10	1	10	9
Female, 286 days	10	1	10	9
Female, 288 days	10	1	10	9
Female, 290 days	10	1	10	9
Female, 292 days	10	1	10	9
Female, 294 days	10	1	10	9
Female, 296 days	10	1	10	9
Female, 298 days	10	1	10	9
Female, 300 days	10	1	10	9

Number of Total... in 1960... patients... are some from... of Seoul,... ents in... than no. of patients... only one third of severe... Therefore, it could be estimated... 2,000 cases of... include moderate and... learn that no. of... is increasing... from... rural... were occurred in... concerned... provinces... province... difficult... serological... endemic... epidemic... where... of... Virus... full... entire... reference... laboratory... from... however... introduced... to... reported... Many... H.I.V....

... 1960... patients... are some from... of Seoul,... ents in... than no. of patients... only one third of severe... Therefore, it could be estimated... 2,000 cases of... include moderate and... learn that no. of... is increasing... from... rural... were occurred in... concerned... provinces... province... difficult... serological... endemic... epidemic... where... of... Virus... full... entire... reference... laboratory... from... however... introduced... to... reported... Many... H.I.V....

disease to discover the causative agent of Korean hemorrhagic fever in Korea 10-15 years since World War but they do not mention about a possibility of outbreak of these diseases. It is surprising to know that about one third of total sera from suspected HFRS patients were HFRS and one third of them are leptospirosis and scrub typhus. We do not know how many cases of leptospirosis and scrub typhus have occurred among US soldiers stationed in Korea because such diagnostic serologic tests were never requested by American doctors from US Army Hospital in Seoul. It is interesting and surprising to know that epidemics of leptospirosis and scrub typhus occurred during epidemic seasons of HFRS in Korea for several years although limited micro-epidemics of HFRS were carried out by us recently. Further studies of micro-epidemic foci, reservoir hosts of the diseases and vectors of scrub typhus in Korea are urgently demanded. Leptospirosis and scrub typhus are very important military diseases for both Korean and US soldiers as well as for farmers. Usually outbreaks of scrub typhus occur in late August after heavy rains and typhus among farmers, and outbreaks of HFRS and scrub typhus occur in October-December every year.

Recent studies have demonstrated a wide geographical distribution of hantaviruses among Asian countries. The origin of this or similar hantaviruses among wild rodents, shrews and genera of small mammals (14-16, 20, 21) and the distribution of hantavirus HFRS is widely distributed and occurs in a variety of different ecological settings. It is well known that hantaviruses cause human disease, especially in Korea where HFRS has not been traditionally recognized as a military infection. As WHO Collaborating Center for HFRS, we have provided serological diagnosis for suspected HFRS patients throughout the world. In addition, we have organized a number of investigators conducting research on the epidemiological evidence of hantavirus infection and distribution among wild urban rats. Results of these efforts have demonstrated that human disease due to hantavirus infection occurs in Korea where HFRS has not been traditionally recognized. Those who used of clinical diagnosis of HFRS in Korea have no question about the relationship between HFRS and hantavirus infection. It is well known that hantaviruses are distributed in a variety of animals including shrews, rodents and other mammals. HFRS is not known to occur in any wild animal in the world (30-31).



Further studies are needed to confirm our results in other areas of HFRS in Euro-Asia where severe form of HFRS patients occur.

It is clear now that IgG antibodies are strain specific, and antibodies are type specific and monoclonal antibodies are strain specific. Among the seroepidemiological tests of HFRS, IF antibody technique is the method of choice for screening test for Hantavirus infections, demonstration of IgM antibodies against Hantaan, Seoul and Puumala viruses in sera from the patients, by ELISA and IPAT are recommended serologic diagnostic test for HFRS and PRNP is the least specific and sensitive test for differentiation of infections with serotypes of Hantaviruses in man and animal. ELISA test is a very sensitive test than IPAT although it is not type specific and it could be very useful for a large scale sero-epidemiological survey for HFRS since ELISA antibodies were detected in sera from HFRS patients 17 years after illness. Seoul and Hantaan viruses isolated from urban rats caught in Hong Kong and in Singapore by ELISA were a little different from prototype strains of Seoul virus by functional antibody assay and were the show of pathogenicity of these viruses in man yet although we have documented HFRS patients in Hong Kong and Singapore. It is an urgent subject to find out an animal model suitable for study of pathogenicity of hantaviruses to man.

#### Summary

1. There were 776 hospitalized Hantaan virus patients and nosed at our laboratory in 1969. 100% of the cases were HOK Hong Kong type and 100% of the cases were HOK type respectively.
2. Epidemics of Hantaan virus infections were observed during epidemic season of Hantaan virus and nos. of patients were 214 and 64, respectively.
3. A rapid assay for Hantaan virus in sera of Hantaan virus patients of Hantaan virus infection was developed by using a mouse anti-Hantaan virus serum. The sensitivity of the assay was 100% and specificity was 100%. A total of 100 sera from Hantaan virus patients were tested and 100% of the sera were positive for Hantaan virus. The sensitivity of the assay was 100% and specificity was 100%. A total of 100 sera from Hantaan virus patients were tested and 100% of the sera were positive for Hantaan virus.
4. Seoul virus is a strain of Hantaan virus and the most characteristic clinical features are fever, headache, abrupt onset of renal dysfunction and hepatic dysfunction, and acute renal failure.
5. Abortion of a fetus was observed in a patient with infection of Hantaan virus and the fetus was found to be infected.

6. If an agent is identified as a potential hazard, the following steps should be taken:
    - a. Determine the nature of the hazard.
    - b. Determine the extent of the hazard.
    - c. Determine the potential for harm.
    - d. Determine the appropriate control measures.
  7. Give special attention to the hazards of urban air pollution. The following steps should be taken:
    - a. Determine the nature of the hazard.
    - b. Determine the extent of the hazard.
    - c. Determine the potential for harm.
    - d. Determine the appropriate control measures.
- cells and the viral strains are genetically from protective measures of the assay.



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