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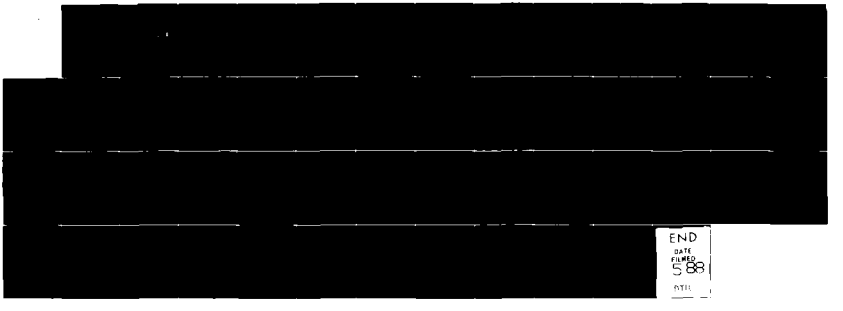

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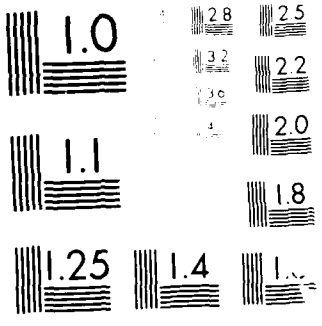
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HEMORRHAGIC FEVER WITH RENAL SYNDROME (KOREAN HEMORRHAGIC FEVER)

ANNUAL SUMMARY REPORT

... KANG LEE, M.D.

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

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 rats and laboratory rats are also reservoirs of HFRS in many parts of the world.

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.

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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 occured 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. interogans. 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 occured 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.

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.

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 occured 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. interogans.

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.

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.

IFAT and Elisa are sensitive and rapid seroepidemiological tools for survey of HFRS and PRNT is specific test for serotyping of Hantavirus infection. IF, Elisa and PRN antibodies persisted 17 years after illness.

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. (NIH) 78-23, Revised 1978).

TABLE OF CONTENTS

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 Nephropathia epidemica (NE), were reported among British soldiers stationed in Flanders during World War I (4), and about 16,000 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, 600 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 1976 from Apodemus mice (8) and isolated from patients in 1978 (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 South and North Korea (11). Antigenic, genetic properties and RNA fingerprints indicated that Hantavirus is a new genus of Bunyaviridae (12,13,14,15). A close etiological relationship was established between EHF and HFRS in USSR, NE in Scandinavia and EHF in Eastern Europe, Japan and China (9,16,17,18). The working group on HFRS at a WHO meeting in Tokyo, 1982 recommended that the above mentioned diseases with different names should be referred to as "Hemorrhagic Fever with Renal Syndrome (HFRS)" (19). Recent seroepidemiologic surveys showed that hantaviruses are ubiquitous in the world. Antibody against hantaan virus in human sera were demonstrated in India, Thailand, Sri Lanka, Brazil, Bolivia, Brazil, Gabon and Republic of Central African (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 among cage-mates 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 mice (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

mental use.

Hantaviruses

All experimental and [illegible] work were done [illegible] E-6 and A549 cells infected with Hantaan virus, strains [illegible], Lee and Hub/9/80 isolated from [illegible] and [illegible] Vero E-6 cells and Seoul virus, strains 80/39 and 82/ [illegible] from Seoul and Incheon urban rats in Vero E-6 cells and [illegible] 82/17 isolated from a Japanese urban rat in Wistar rat [illegible] adapted in Vero E-6 cells. To titrate the virus from rat lungs, 10% lung suspensions are prepared with [illegible] containing [illegible] bovine albumin clarified at 5,000 G for 20 min. at 4°C and supernatants are used as inoculum. The [illegible] of strains [illegible] and Lee in [illegible] mice [illegible] and [illegible] of strains 80/39 and [illegible] 82/17 in Wistar [illegible] and [illegible], respectively. All strains of [illegible] Seoul [illegible] from [illegible]. [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible] described [illegible].

RESULTS

A. New epidemiological features of the [illegible] outbreak leptospirosis and rickettsiosis during [illegible] epidemic year of HFRS in Korea.

1. New epidemiologic features of HFRS

There were 766 hospitalized cases of [illegible] confirmed serologically at our institute in 1986 and 10 of them were U.S. 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 90 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 increasing no. of cases of HFRS among children and male patients are dominant group as shown in Table 6 although [illegible] soldier patients were 18 [illegible] cases in the no. of the cases. Table 7 shows occupation of HFRS among HFRS patients in different localities and clinical features of the patients were as shown in Table 8 and 9. Total occurrence of HFRS among civilians, ROK Army and U.S. Army are shown in Table 7.

2. [illegible] outbreaks of leptospirosis and rickettsiosis during epidemic season of HFRS

As shown in Table 6, total no. of confirmed cases of HFRS in 1986 is 766 among 2,067 HFRS suspected sera tested. These suspected sera were sent to our laboratory from hospitals in 8-9 nearby cities of Seoul for serologic diagnosis of HFRS but HFRS was only 36% of total patients. During epidemic season of HFRS, we have tested 1,553 sera from suspected HFRS patients for leptospirosis and confirmed 64 cases of leptospirosis serologically and clinically. Incidence of leptospirosis was shown in Table 9. No. of leptospirosis patients [illegible] soldier and 18 Army soldiers were as shown in Tables 10 and 11. We have tested 69 [illegible] non-leptospirosis sera during rickettsiosis and 21 [illegible] among these unknown patients were scrub typhus and tsutsugamushi. There were 10 cases of HFRS patients [illegible] HFRS. Suspected sera from 78 soldiers hospitalized [illegible] Army hospital in Seoul and we did test some of these HFRS sera against leptospira and rickettsia and confirmed leptospirosis and one serum typhus as shown in Table [illegible] distribution of HFRS, leptospirosis and scrub typhus in Korea in 1986 is shown in Table 12 and three [illegible] the patients were recruited in Kyonggi, 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	28	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	[illegible]	246
1965	99	110	[illegible]	211
1966	36	82	[illegible]	129
1967	31	66	[illegible]	130
1968	26	102	[illegible]	156
1969	9	134	[illegible]	191
1970	13	221	[illegible]	345
1971	2	556	[illegible]	741
1972	0	203	[illegible]	389
1973	0	337	[illegible]	478
1974	0	251	176	427
1975	1	370	[illegible]	857
1976	4	504	[illegible]	893
1977	7	241	[illegible]	536
1978	10	168	[illegible]	385
1979	1	122	[illegible]	364
1980	1	72	[illegible]	256
1981	2	164	377	543
1982	3	123	[illegible]	504
1983	3	68	432	503
1984	3	156	[illegible]	730
1985	7	159	531	697
1986	10	166	[illegible]	706
Total	2,949	5,940	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							
	1980	1981	1982	1983	1984	1985	1986	Total
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
Kyungsangdo	17	6	14	23	21	20	29	130
Cholradc	6	7	7	16	24	30	29	119
Total	185	377	378	402	568	531	540	2,971

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	1	4	6	0	3	4	1	3	15	34	15	91
1985	6	1	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
Eunpyung-ku	3	3	4	4	2	5	21
Kuro-ku	3	0	4	8	9	10	34
Yungdungpo-ku	9	4	0	4	2	3	22
Kwanak-ku	6	5	2	4	5	9	31
Kangnam-ku	6	14	3	10	5	5	43
Kangdong-ku	4	5	4	6	7	4	30
Dongjzak-ku	3	0	1	6	1	2	13
Kangseo-ku	2	1	0	8	5	11	27
Total	65	73	46	91	70	93	438

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	46	33	111	156	319	112	893
1977	7	0	0	2	8	57	21	19	29	93	226	74	536
1978	17	8	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	14	6	4	8	14	11	5	5	6	40	74	62	250
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	8	19	22	24	24	14	25	114	213	186	706
Total	399	110	79	126	241	410	319	242	410	1,789	3,855	2,025	10,005

Table 6.
Occurence 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
Kyunggido,		Dongducheon	1
Paju	31		
		Kangwondo,	
Pocheon	19	Chulwon	31
Kimpo	16	Inje	8
Yeoncheon	11	Whacheon	7
Yangju	7	Koseong	3
Kangwha	1	Hongcheon	2
Koyang	2	Yangyang	1
Suwon	1	Wheongseong	2
Kapyung	1	Samcheok	1
Whaseong	1	Kimwha	1
Shineung	1	Kangseong	1
Ilsan	2	Sokcho	1
Songchu	1	Chungcheongnamdo,	
		Nonsan	1
Incheon	1		
		Kyungsangnamdo,	
Dukjeong	2	Tongyoung	1
Wondang	1	Kyungsangbukdo,	
		Youngdong	1
Icheon	1		
		Chullabukdo,	
Pyungtaek	1	Buann	1
		Goonsan	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

Month	No. of antibody positive sera against Hantaan virus / No. of tested sera from suspected patients			
	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	18/85	6/14	0/1	24/99
7	19/93	5/12	0/3	24/105
8	12/80	1/6	1/2	14/88
9	24/114	[illegible]	1/1	25/131
10	[illegible]	[illegible]	0/3	114/384
11	145/394	63/91	5/20	213/505
12	160/310	24/34	2/6	186/355
[illegible]	530/1,[illegible]	[illegible]/291	10/38	706/2,074
No. of [illegible]	?	6	2	
[illegible]		4.6 %	20 %	

Table 3.
Number of HFRS, Leptospirosis and Scrub typhus patients diagnosed serologically among hospitalized suspect [illegible] patients at the Institute for Viral Disease, Korea University

1985		1986	
Total no. of HFRS	697	Total no. of HFRS	706
Total no. of serum tested	2,136(33%)	Total no. of serum tested	2,068(34%)
Total no. of leptospirosis	43	Total no. of leptospirosis	64
Total no. of serum tested	1,554(2%)	Total no. of serum tested	1,593(4%)
Total no. of scrub typhus	129	Total no. of scrub typhus	215
Total no. of serum tested	1,233(11%)	Total no. of serum tested	692(31%)
Total no. of unknown patient	948	Total no. of unknown patient	948
Total no. of serum tested	2,136	Total no. of serum tested	2,068(46%)

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

Month	HFRS			Leptospirosis			Scrub typhus		
	M	F	Total	M	F	Total	M	F	Total
1	24/72[V]	6/44	30/116	14/70	4/40	18/110	n.t.	n.t.	n.t.
2	10/[illegible]	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/[illegible]	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	3/2[illegible]	19/93	1/61	0/18	1/79	n.t.	n.t.	n.t.
8	8/[illegible]	4/23	12/[illegible]	1/[illegible]	0/13	1/39	n.t.	n.t.	n.t.
9	15/[illegible]	5/30	2[illegible]/[illegible]	6/[illegible]	2/30	8/114	n.t.	n.t.	n.t.
10	[illegible]/[illegible]	[illegible]/[illegible]	76/[illegible]	[illegible]/[illegible]	2/151	7/[illegible]	25/69	48/92	73/[illegible]
11	101/221	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	388/[illegible] ([illegible]%)	144/647 ([illegible]%)	530/1,755 (30.2%)	45/814 (5.5%)	13/513 (2.5%)	58/1,327 (4.4%)	62/292 (28.1%)	108/346 (31.2%)	170/638 (26.6%)

[V] : No. of serologically confirmed patient
No. of suspected patient tested

Table [illegible]
Number [illegible] confirmed hospitalized cases of HFRS, Leptospirosis and Scrub typhus among [illegible] villagers in the [illegible] Area, Kwon-ju University in Korea, 1986

[illegible]	HFRS	Leptospirosis	Scrub typhus
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	n.t.
[illegible]	[illegible]	[illegible]	3/3
[illegible]	[illegible]	[illegible]	4/7
[illegible]	[illegible]	[illegible]	0/3
[illegible]	[illegible]	[illegible]	7/13 (53.9%)

Table 1.
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[V]	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

[V] : 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
Kyounggi-do	238	20	92
Kangwon-do	46	3	15
Chungchoungbuk-do	27	4	18
Chungchoungnam-do	54	5	15
Jeollabuk-do	26	5	9
Jeollanam-do	3	1	5
Kyoungsangbuk-do	14	1	0
Kyoungsangnam-do	9	0	0
Total	535	58	170

Table [illegible].
Age and sex distribution of [illegible], leptospirosis and scrub typhus in Korea, 1986

Age	[illegible]			Leptospirosis			Scrub typhus		
	M	F	Total (%)	M	F	Total (%)	M	F	Total (%)
0 - 10	[illegible]	0	[illegible]	0	0	0	1	1	1(0.6)
11 - 20	20	8	28 (5.3)	2	0	2(3.4)	1	1	2(1.2)
21 - 30	[illegible]	21	[illegible]	5	0	5(8.6)	4	11	15(8.8)
31 - 40	[illegible]	[illegible]	[illegible]	9	2	11(19.0)	9	5	14(8.2)
41 - 50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	12(20.7)	13	19	32(18.8)
51 - 60	[illegible]	[illegible]	[illegible]	14	2	16(27.6)	13	36	49(28.8)
61+	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	21	35	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	43	12	58	62	108	[illegible]
	[illegible]	[illegible]		(74.6)	(22.4)		(36.5)	(63.5)	

[illegible]-do. It is noteworthy that about 54% of scrub typhus patients was female and 60% of the patients were in age group of 40-60, but more 75% of leptospirosis patients was male in age group of 30-60 as shown in Table 15.

3. [illegible] Survey of wild rodents with hantavirus, leptospira and R. tsutsugamushi in Korea, 1986.

It is known that hantaan and seoul viruses in the Genus Hantavirus, leptospira interogans javanica 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, Microtus mice and rats 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 Kwacheon, an endemic area of HFRS from June to December 1986. As shown in Table 14, 14% of 230 A. agrarius mice and 30% of 157 house rats were seropositive against hantavirus, 9% of 11 A. speciosus mice, 3 out of 8 M. montebelli mice, and 21% of 14 house rats were seropositive against leptospira javanica. Sixty-eight of 190 A. agrarius mice, 3 out of 4 M. montebelli mice, and 5 of 139 house rats were seropositive against R. tsutsugamushi. The infection rate of hantaan virus in house rats with hantavirus in Korea is almost the same as found previously, but the HFRS infection rate of field mice and house rats with leptospira and rickettsia is very low. Table 15,16, and 17 show the rate of number of [illegible] infection with hantavirus, L. [illegible] and R. tsutsugamushi in wild rodents. As it is [illegible] mice, 1-7% of urban rats and some of Microtus mice were proved to be [illegible] with all of three agents based upon the identification of the infected at the same time. It can be speculated that there will be more cases of HFRS in urban areas than that of cases of leptospirosis and scrub typhus in [illegible] years [illegible] increased by rickettsia, and [illegible] for scrub typhus [illegible].

Table 14.
Epidemiologic survey of infected rodents with hantavirus, Leptospira [illegible] in Korea, 1986

Location	Date	No. of rodents examined	No. of seropositive rodents (%)	
		Hantavirus	Leptospira	Scrub typhus
Kunnammyeon, Yeonchunkun,	23 - 25 June	2/34	0/34	n.t.
"	27 - 31 Oct.	0/57	8/57	42/57
"	3 - 6 Nov.	0/46	5/46	34/46
Chuksungmyeon, Pajukun,	17 - 21 Nov.	[illegible]	5/45	27/45
Wuncheonmyeon, Pochunkun	9 - 14 Dec.	0/48	3/48	36/48
Total		[illegible]	21/230(9.1)	139/196(70.9)
Kunnammyeon, Yeonchunkun,	27 - 31 Oct.	1/	2/6	5/6
"	3 - 6 Nov.	[illegible]	[illegible]	[illegible]
Total		[illegible]	[illegible]	[illegible]
Chuksungmyeon, Pajukun,	17 - 21 Nov.	[illegible]	[illegible]	[illegible]
Wuncheonmyeon, Pochunkun	9 - 14 Dec.	[illegible]	[illegible]	[illegible]
Total		[illegible]	[illegible]	[illegible]
Samchuk city	9 - 14 June	[illegible]	[illegible]	[illegible]
Ansan city	21 - 25 July	[illegible]	[illegible]	[illegible]
Hison city	18 - 22 Aug.	[illegible]	[illegible]	[illegible]
Pusan city	[illegible] - 5 Sept.	[illegible]	[illegible]	[illegible]
Sokcho city	22 - 27 Sept.	[illegible]	6/14	9/14
Mokpo city	20 - [illegible] Nov.	[illegible]	[illegible]	2/3
Yeosu city	24 - 28 Nov.	[illegible]	0/29	[illegible]
Wuncheonmyeon, Pochunkun,	9 - 14 Dec.	[illegible]	9/31	[illegible]
Total		[illegible]	[illegible]	[illegible]

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

Location	Date of collection	No. of antibody positive/no. of mice tested						
		H[1]	R[2]	L[3]	H+R	H+L	R+L	H+R+L
Yeoncheon	June '86	2/34	n.t.	0/34	n.t.	n.t.	n.t.	n.t.
Yeoncheon	Oct. '86	9/57	42/57	8/57	2/57	0/57	3/57	4/57
Yeoncheon	Nov. '86	6/48	34/48	5/48	4/48	0/48	5/48	0/48
Poju	Nov. '86	14/45	27/45	5/45	10/45	0/45	1/45	2/45
Wonchoon	Dec. '86	0/16	30/46	3/46	0/46	0/46	1/46	0/46
Total		31/239 (13%)	133/196 (68%)	21/230 (9%)	16/196 (8%)	0/196	10/196 (5%)	6/196 (3%)

[1] : Hantavirus (HTN)
[2] : Rickettsia tsutsugamushi (Kato)
[3] : Leptospira interogans serovar hebdomadis (Kito)

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	H+R	H+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	6/20	0/20	3/20	0/20	0/20
Sokcho	Sept.'86	3/14	0/14	2/14	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	2/16	2/16	0/16	1/16	0/16	0/16	0/16
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%)	33/157 (21%)	3/139 (2%)	10/139 (7%)	1/139 (1%)	1/139 (1%)

HV : Hantaan Virus 76/118 (FRA)
RV : R.tsutsugamushi Kato Gilliam 56 K (IFAT)
LV : Leptospira interrogans 56 K (MIsa)

Table 17.
Antibody test of wild urban rats 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 rats tested						
		HV	RV	LV	H+R	H+L	R+L	H+R+L
Yeoncheon	Oct. '86	6/6	2/6	2/6	2/6	2/6	1/6	1/6
Yeoncheon	Nov. '86	3/3	1/3	1/3	1/3	0/3	0/3	0/3
Total		9/9 (100%)	3/9 (33%)	3/9 (33%)	3/9 (33%)	2/9 (22%)	1/9 (11%)	1/9 (11%)

HV : Hantaan Virus 76/118 (FRA)
RV : R.tsutsugamushi Kato Gilliam 56 K (IFAT)
LV : Leptospira interrogans 56 K (MIsa)

B. Global serologic surveys for the [illegible] virus 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 16. 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, and [illegible] and Sri Lanka.

Urban rat sera from the Philippines, Hong Kong, Malaysia, Singapore, Fiji, [illegible], Sudan and Uganda were also found to have IF antibodies to Hantaan virus with a high prevalence rate of 61.8% in the Philippine rats and 20.0% in Egypt rats.

Laboratory-bred white rats from Malaysia, Hong Kong, Singapore, Hawaii and Argentina were IF-positive against Hantaan virus. Five out of 11 [illegible] rats from Egypt and 4 out of 30 Calomys rats from Argentina were also positive to Hantaan virus. Clearly the [illegible] virus has a near global distribution and [illegible] a variety of different ecological settings. The [illegible] which mainly does cause human disease, appears [illegible] 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		Mice
Hong Kong	16/322[1]	(5.0%)	26/140[5]	(18.6%)	3/62	(4.8%)	0/40
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[2]	(9.5%)	6/52	(11.5%)	5/38	(13.2%)	
Taiwan	31/240[3]	(13.0%)					
India	1/89	(1.1%)					
Sri Lanka	11/155[4]	(7.1%)	[illegible]				
Fiji	8/145	(5.5%)	[illegible]				0/3
Hawaii	15/252	(6.0%)	[illegible]		[illegible]		0/22
Egypt	9/458	(1.9%)	[illegible][6]				5/71 (7.0%)
Sudan			28/352	(8.0%)			
Uganda	15/355	(4.2%)	3/64	(4.7%)			
Brazil	37/500	(7.4%)					
Argentina	15/300	(5.0%)	0/31		11/102	(10.7%)	4/30 (13.3%)
Paraguay	8/805	(1.0%)					
Bolivia	2/28	(7.1%)					
Canada	29/2,063	(1.4%)					

[1] : 4 HFRS patients
[2] : 1 HFRS patient
[3] : 2 HFRS patients
[4] : 1 HFRS patient and died

[5] : Isolated Seoul virus-like virus
[6] : Isolated Seoul virus-like virus
[7] : 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 KHF, 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 exit. 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 [illegible] patients, who were diagnosed as having hepatitis, included fever, chills, jaundice, thrombocytopenia, proteinuria, and abnormal liver and renal function. Renal involvement, which is characteristic of HFRS, was mild. A prominent finding was marked elevation of serum transaminases suggestive 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[1]	China[2]	Japan & Korea[3]	Finland[4]
Fever	100%	100%	100%	100%
Anorexia	-	-	[illegible]	70
Chills	92	-	10	60
Nausea	62	72	[illegible]	70
Vomiting	63	58	[illegible]	70
Backache	55	-	[illegible]	30
Myalgia	70	69	[illegible]	40
Headache	80	83	[illegible]	60
Abdominal pain	25	25	[illegible]	50
Constipation	30	-	[illegible]	20
Diarrhea	11	11	[illegible]	10
Dizziness and Vertigo	100	42	[illegible]	10
Ophthalmalgia	-	33	[illegible]	5
Blurred vision	-	13	-	10
Conjunctival injection	64	25	[illegible]	10
Pharyngeal or palatal injection	55	64	[illegible]	[illegible]
Petechiae on body	32	58	[illegible]	[illegible]
Hemorrhages (hematemesis, epitaxis, melena, etc.)	72	54	[illegible]	[illegible]
Hepatomegaly	5	-	[illegible]	[illegible]
Splenomegaly	1	-	[illegible]	[illegible]
Lymphadenopathy	30	[illegible]	[illegible]	[illegible]
Preorbital edema	5	17	[illegible]	[illegible]
Proteinuria	96	-	[illegible]	[illegible]
Hematuria	85	88	[illegible]	[illegible]
Oliguria $\leq$ 500 ml	67	[illegible]	[illegible]	[illegible]
Polyuria > 2000 ml	9	[illegible]	[illegible]	[illegible]
Leukocytosis > 10000/mm^3	91	[illegible]	[illegible]	[illegible]
Thrombocytopenia < 100000/mm^3	95	78	[illegible]	[illegible]
Increased ESR > 20mm/h	72	-	[illegible]	[illegible]
BUN > 20 or Crtnn > 2 mg/dl	94	[illegible]	[illegible]	[illegible]
Hypotension (< 90/60 mmHg)	60	[illegible]	[illegible]	[illegible]

[1] : Counts and Seltser, 40 [illegible]
[2] : Cohen, et al. 7% cases [illegible]
[3] : Morimoto, et al. 27 cases [illegible]
[4] : Lähdevirta, 76 cases (19[illegible])

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 28), she developed uterine bleeding and subsequently delivered a 3.3 Kg fetus which died 11 hours after birth. Autopsy revealed variable degrees of hemmorrhage in the kidneys, heart, lungs, and adrenal glands similar to the pathologic findings in adults with fatal HFRS (44).

The IgG immunofluoresecent 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 of 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.

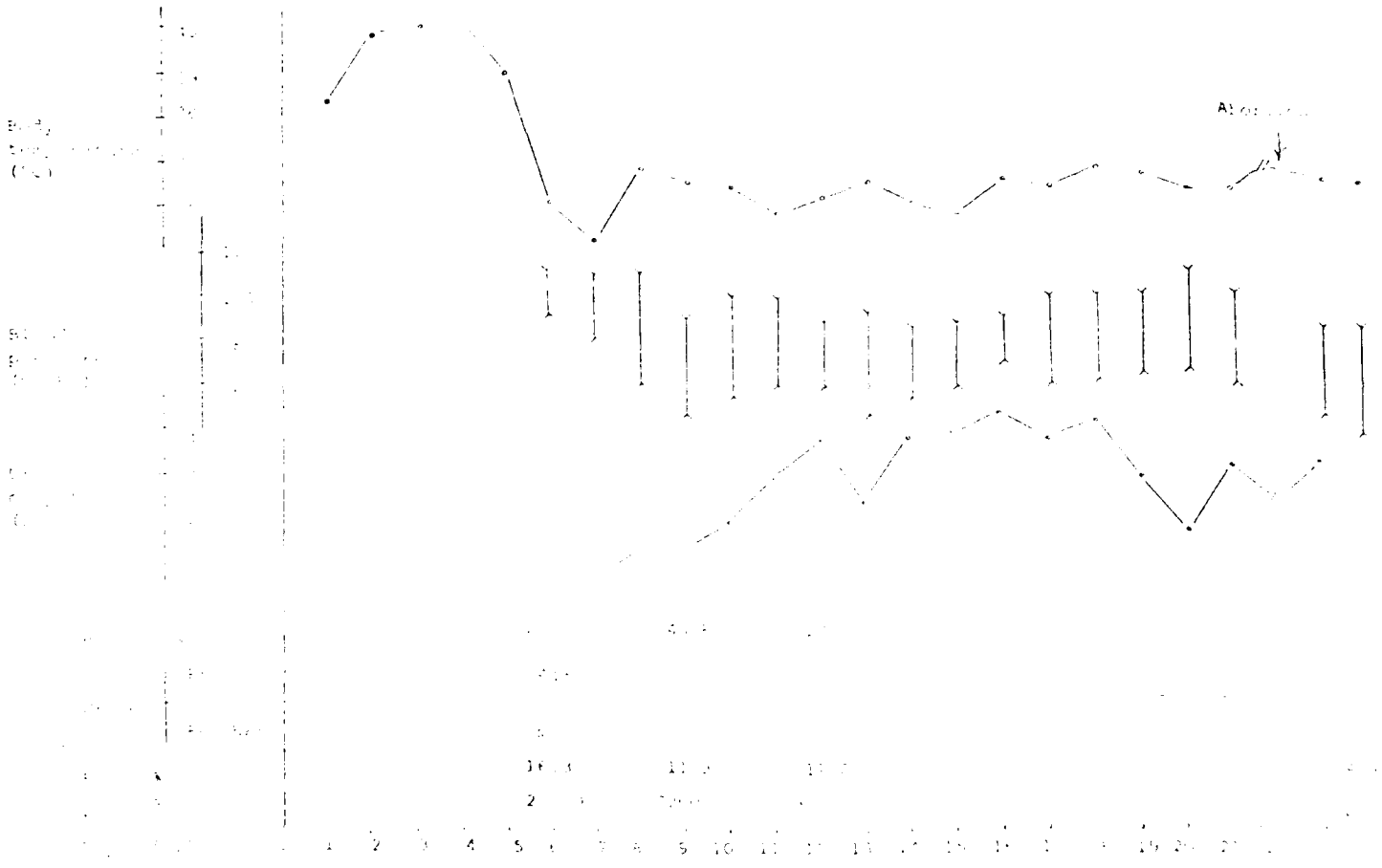
Liver: The lobular architecture was well preserved. Large numbers of hematopoietic cells were noted in the sinusoidal spaces. The hepatocytes and bile ducts were unremarkable.

Adrenals: There was diffuse cortical hemorrhage and severe thickening of the cortical layer. The cortical cells exhibited swollen eosinophic 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 intact. The white pulp was well preserved. The medullary spaces were markedly congested with evidence of focal hemorrhage and extramedullary hematopoesis.

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



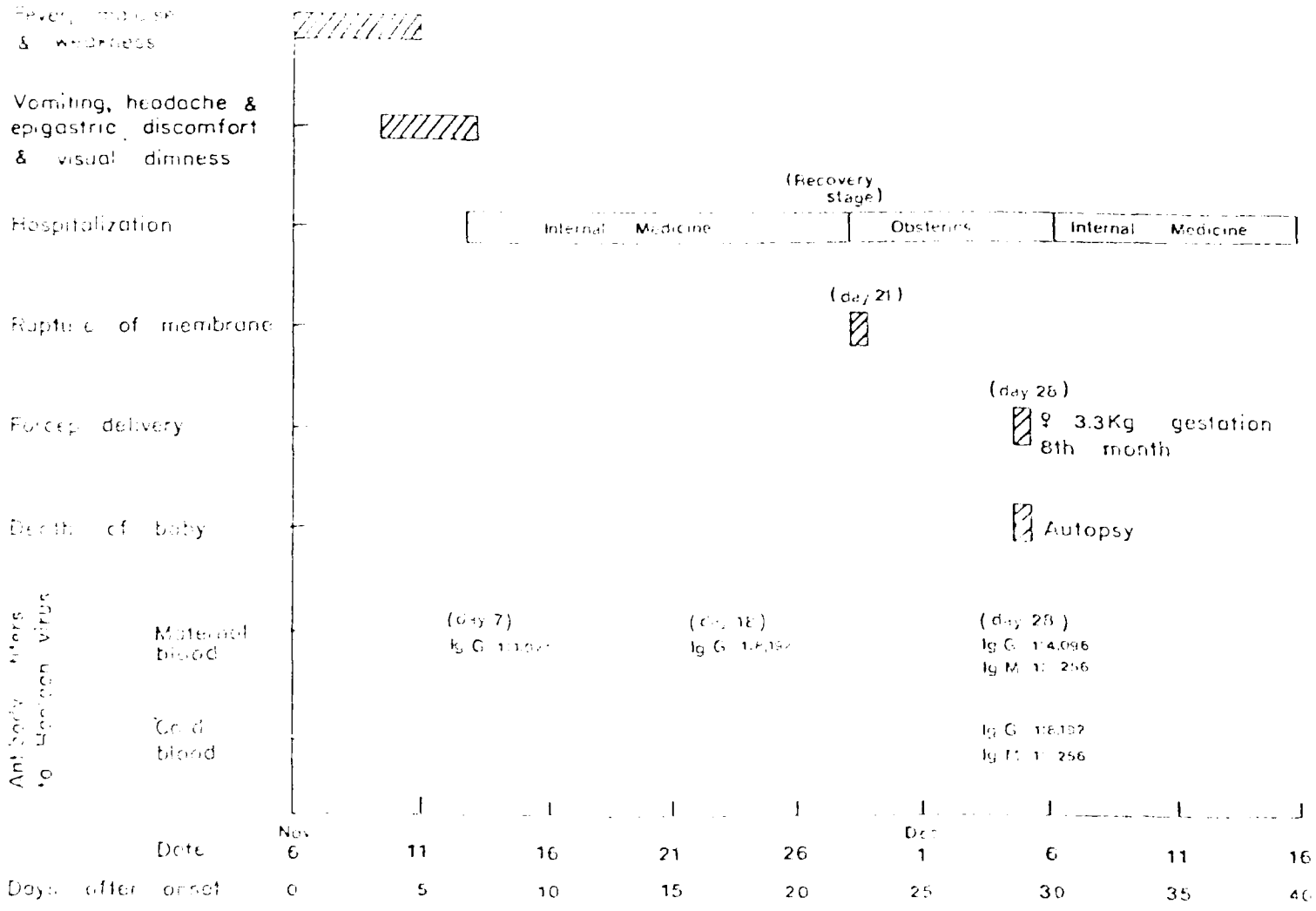


Fig. 2. Vertical transmission of Hantaan virus in a pregnant woman (28 years, 8th month of pregnancy)

E. Comparative sensitivity [illegible] diagnosis of HFRS and the [illegible]

The available serologic [illegible] HFRS are the indirect IF antibody technique (IFAT), [illegible] antibody test, IAHA test and plaque reduction neutralization test (PRNT). IFAT and Elisa are very sensitive and rapid. [illegible] 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 [illegible] no IgM antibodies were detected. [illegible] were 5-50 times higher than IF and neutralizing antibodies. IF, ELISA and PRNT antibodies persisted for as long as 17 years after illness. PRNT is sensitive [illegible] for the infecting serotype virus. This test confirmed that 5 of the 7 past HFRS patients were infected with Hantaan virus and 2 with Seoul virus. These patients had [illegible] titers of IF antibodies but high titers of [illegible] PRNT antibodies against the infecting virus. As one of the more 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 [illegible] of antibodies against Hantaan virus exist in human and animal sera. We have tested 15 sera from healthy [illegible] that contained IF antibodies (titers between 16-64) [illegible] PRNT with Hantaan and Seoul viruses, and Hantaan virus with Seoul virus. The results were negative with these techniques as shown in Table 21. This suggests that there are other non-specific IF antibodies in rat sera against Hantaan or rat viruses, or unknown agents related to 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 Hantaan and Seoul virus of sera from [illegible] staff of the Institute for Viral Diseases, Korea University by different serologic diagnostic tests

Name	Years after illness	IFA test Titer IgM	IgG	ELISA test Titer IgM	IgG	PRNT Titer Hantaan	Seoul	Infection history
[illegible], C.A.	17	2[illegible]	-	12[illegible]	-	4[illegible]	6[illegible]	field [illegible]
[illegible], C.W.	10	1[illegible]	-	12[illegible]	-	10[illegible]	<[illegible]	[illegible]
[illegible], I.J.	8	32	-	6[illegible]	-	2[illegible]	1[illegible]	[illegible]
[illegible], C.I.	7	2[illegible]	-	[illegible]	-	1[illegible]	[illegible]	field [illegible]
[illegible]	[illegible]	1[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 23.

disease [illegible] hemorrhagic fever in Korea [illegible] years since [illegible] but they did 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 occured 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 occured during epidemic seasons of HFRS in Korea for several years although limited [illegible] carried out by us recently. Further studies of [illegible], reservoir hosts of the disease and vector of Scrub typhus in Korea are urgently needed [illegible] prevention of the diseases. Leptospirosis and Scrub typhus are very important military diseases for both Korean and US soldiers as well as for human. Usually, outbreak of [illegible] in late August after heavy rains and cyclones, [illegible] and outbreak of HFRS and Scrub typhus occur in October-December every year.

See [illegible] distribution of [illegible] among [illegible] this of small mammals [illegible] and genera of small mammals [illegible] Hantavirus [illegible] is widely distributed [illegible] of different ecological settings [illegible] Hantaviruses cause human disease [illegible] has not been established [illegible]. As WHO Collaborating Center [illegible] provided serological diagnosis for [illegible] throughout the world. In addition, we have [illegible] number of investigators conducting [illegible] prevalence of Hantavirus infection [illegible] human rats. Results of these [illegible] human disease due to [illegible] where HFRS has not been [illegible] who died of [illegible] serologically [illegible] no question about the [illegible] clinical [illegible] preliminarily [illegible] rent variety of clinical [illegible] patients in Seoul [illegible] HFRS is not known to [illegible] evidences about [illegible] animals with Hantaviruses in many [illegible] of the world [30-34].

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

It is clear now that IF antibodies are virus specific, the antibodies are type specific and some cross antibodies are strain specific. Among the seroepidemiological tools 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 MFISA and IFAT are recommended serological diagnostic test for HFRS and PRNT is the most specific and sensitive test for differentiation of infection with serotypes of Hantaviruses in man and animal. ELISA test is a very sensitive test than IFAT although it is not type specific but it could be very useful for a large scale sero-epidemiological survey for mice since ELISA antibodies titer persists from HFRS patients 17 years after illness. Seoul virus is a virus isolated from urban rats caught in many ports and in Singapore it was a little different from prototype strain of rats. With a monoclonal antibody assay and the knowledge of geographical distribution of these viruses in man we have documented HFRS patients in Hong Kong and Singapore. It is an urgent subject to find out an ideal host animal for the study of pathogenesis of Hantaviruses in man.

Objectives

1. [illegible] with 700 hospitalized [illegible] patients diagnosed as Viral Hepatitis in [illegible] Hong Kong respectively.
2. [illegible] of acute [illegible] sera collected during epidemic season of [illegible] and 88 of patients were 21% and 6% respectively.
3. [illegible] Hong Kong, [illegible] of Hantaan virus [illegible] of hospitalized [illegible] in Korea. [illegible] of 17 house rats were [illegible] of 190 [illegible] 139 house rats were [illegible] and 5 of 24 [illegible] and 21 of 71 [illegible].
4. [illegible] virus [illegible] and the most clear [illegible] headache, [illegible] reported [illegible].
5. Abortion of a [illegible] transmission of Hantaan [illegible] documented for the first time.

6. [illegible]

7. [illegible]
of urban [illegible]
cells and [illegible]
genically from [illegible]
assay.

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