Virus Name: Hantaan		Abbreviation: HTNV
Status **Possible Arbovirus**	Select Agent **No**	SALS Level **3**

SALS Basis
Results of SALS surveys and information from the Catalogue.

Other Information
DOC Permit Required, USDA Restricted

Antigenic Group
3

SECTION I - Full Virus Name and Prototype Number

Prototype Strain Number / Designation
76-118

Accession Number

Original Date Submitted
10/15/1984

Family
Bunyaviridae

Genus
Hantavirus

Information From
G.R. French and H.W. Lee , Revised by T.F. Tsai, J.M. Dalrymple, N. Karabatsos.

Address
USAMRIID, Frederick, MD 21701 and Korea University Medical College Seoul KOREA

Information Footnote

Section II - Original Source

Isolated By (name)
Ho Wang Lee, et al (1)

Isolated at Institute
Seoul, Korea

Host Genus
Apodemus agrarius coreae (rodent)

Species

Host Age/Stage
Adult

Sex
Male

Isolated From	Isolation Details
Organs/Tissues	**Lung and kidney**

Signs and Symptoms of Illness
None (IF viral antigen in tissues when sacrificed)

Arthropod

Time Held Alive before Inoculation

Collection Method
Trapped

Collection Date
6/23/1976

Place Collected (Minimum of City, State, Country)
Near the Hantaan River, Songnaeri, Kyungido, Korea

Latitude
37° 55' N

Longitude
127° 5' E

Macrohabitat
Near mountains in temperate zone

Microhabitat
[Bank of a field (potato, corn and barley)], near the burrows

Method of Storage until Inoculated
Kept alive until processed

Footnotes

Section III - Method of Isolation

Inoculation Date
7/25/1976

Animal (Details will be in Section 6)
animal

Route Inoculated
IM and intrapulmonary

Reisolation
Yes

Other Reasons
Numerous isolations from this same species.

Homologous Antibody Formation by Source Animal
Yes

Test(s) Used
Indirect and direct IFA

Footnotes

Section IV - Virus Properties

Physicochemical
RNA, Single Strand

Pieces (number of genome segments)
3 (29)

Infectivity

Sedimentation Coefficients(s)
L=2.7x106M(S)

Percentage wt, of Virion Protein

Lipid

Carbohydrate

Virion Polypeptides: Number
4

Details
Nucleoprotein (N): 45-50,000 MW; glycoproteins (G1,G2): 55-56,000 MW, 72,000 MW; (L) 200,000 MW (30)

Non-virion Polypeptides: Number

Details

Virion Density
1.16-1.17; 1.20-1.21 in sucrose; CsCl2

Sedimentation Coefficients(s)
450 S (31)(S)

Nucleocapsid Density
1.19; 1.25 in sucrose; CsCl2

Sedimentation Coefficients(s)
(S)

Stability of Infectivity (effects)

pH (infective range)
Maximum stability at pH 7.6; inactived at pH 3.0

Lipid Solvent (ether - % used to test)
20%

After Treatment Titer
<1.0 dex

Control Titer
6.0 dex

Lipid Solvent (chloroform)
5%

After Treatment Titer
<1.0 dex

Control Titer
6.0 dex

Lipid Solvent (deoxycholate)
0.1%

After Treatment Titer
<1.0 dex

Control Titer
6.0 dex

Other (formalin, radiation)
Inactivated with 70% ethanol or 0.5% iodine; cobalt irradiation at 1.3x107 rads

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Virion Morphology

Shape
Bunyavirus-like (24-28)

Dimensions
80-115 nm

Mean
nm

Range
nm

nm nm

Measurement Method	Surface Projections/Envelope	Nucleocapsid Dimensions, Symmetry
Electron microscopy	**Surface projections, 11-13 nm; lipid envelope**	

Morphogenesis

Site of Constituent Formation in Cell	Site of Virion Assembly	Site of Virion Accumulation
		Cisternae of endoplasmic reticulum (28)

Inclusion Bodies	Other
Seen with immunoperoxidase staining (28)	

Hemagglutination

Hemaggiutination	Antigen Source	Erythrocytes (species used)
Yes	**Apodemus lung tissue or A-549 cell cultures**	**Gander*** **

pH Range	pH Optimum
5.8-7.2	**5.8-6.4**

Temperature Range	Temperature Optimum
4dC, 25dC, 37dC	**25dC**

Remarks
HA obtained with SMB extracted by sucrose-acetone and reacted with gooseRBC's(32) * Proposed genus designation If the virus is handled in rodents, then Level 4. ***In addition to goose, Human O, rhesus monkey, guinea pig RBC's used**

Serologic Methods Recommended
NT, IFA, immune adherence HA, HI

Footnotes
HA obtained with SMB extracted by sucrose-acetone and reacted with gooseRBC's(32) * Proposed genus designation If the virus is handled in rodents, then Level 4. ***In addition to goose, Human O, rhesus monkey, guinea pig RBC's used**

Section V - Antigenic Relationship and Lack of Relationship to Other Viruses

Hantaan virus has been tested against the following NIAID reagent polyvalent antisera by indirect fluorescent antibody (IFA) tests utilizing strain 76-118 infected A-549 cells as substrate. All sera were negative (<1:10) unless otherwise indicated. Group C (Lot 2); GMA gr.; SIM gr.; VSV gr.; BUN gr.; CALgr.; TCR gr.; PHL gr.; polyvalent QRF, KSO, QYB, polyvalent grs. ANA, ANB, TUR; polyvalent BWA, MOS, NDO; polyvalent PAT; CAP gr.; polyvalent PAL, COR, EUB; KEM gr.; polyvalent CON, NSD; polyvalents 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 12; polyvalent rabies, LCM, NDV, herpes, vaccinia; coronavirus (OC-43) and coronavirus (229E).
A weak atypical reaction was repeatedly observed at a 1:20 dilution of the Bunyamwera Group polyvalent MIAF. The following antisera prepared against individual BUN group viruses were tested by IFA with negative results (<1:10):

YARU Antisera	CDC-Ft. Collins Antisera
BUN,BAT,ILE KRI,GRO,TAIASSUI	GER,LOK,WYO,TEN,MAG,SAR SOR,ANH,NOR,CV,BIR,SHO

Of 161 monovalent HIAF raised against viruses of the Bunyaviridae, only the fluid to Anhembi virus reacted by IFA, at a titer of 16, to Hantaan virus [34] .
In addition, a polyvalent monkey anti Lassa-Machupo-Junin serum prepared at USAMRIID titered <10 as did anti-RVF rabbit serum and anti-Congo and anti- Hazara mouse serum. Direct conjugates of polyvalent group A (Alphaviruses) and polyvalent group B (Flavi) were also negative. Similarly, human convalescent sera from Machupo, Lassa, Marburg, and Ebola infections provided by Dr. Karl Johnson were negative when tested by IFA against strain 76-118 infected Apodemus lung sections.
The following virus complement-fixation (CF) antigens were tested by Dr. Robert Shope, YARU against two human KHF convalescent antisera. All CF tests were negative (<8). The human sera had Hantaan IFA titers of 320 and 640. AH, ACD, ACA, AKA, AMA, ANH, ANA, ANB, APEU, ARK, ARU, AMT, Abadina, BAN, BAK, BDA, BGN, BAU, BER, BHA, BLU, BOC, BTK, BUJ, BSB, BUT, BWA, BIA, AP, URU, BLM, CE, CDU, CAP, CHO, CHG, CHP, CGL, CHV, CNU, COC, CTF, CON, COR, COT, CR, Cedros, DEN-2, DGK, DHO, DUG, EEE, EHD, EUB, EgAn1398-61, Eret147, Farallon, FLA, GAM, GER, GA, GJA, GMA, GRO, GI, HAZ, HUA, HUG, ICO, IERI, ILE, IRI, ITP, ITQ, IbH11306, IbAn38918, Ichampadi, JOC, JAP, JOI, JUN, JUR, KK, KRI, KMP, KAN, KS, KAR, KEM, KC, KTR, KOO, KOW, KWA, KSO, KAM, KLA, kotonkan, LB, LJ, LJN, LEB, LD, LS, LUK, LCM, MAL, MAN, MAP, MCO, MTY, MAT, MEL, MNT, MIN, MIR, MOD, MOS, MEB, Mokola, NKO, NOLA, NYM, NDO, OKO, ORI, ORO, ORU, OLI, OYA, Obodhiang, PCA, PAC, PAL, PATA, PIC, PIRY, PT, QYB, QRF, Rabies, REO-3, SAL, SFN, SFS, SAT, SAW, SEM, SF, SIL, SIM, SOL, SLE, GF, TCM, TCR, TAM, TAT, TME, TEN, TETE, THI, THO, TPM, TNT, TUR, TSU, UMB, UPO, UUK, VEE, VSI, VSNJ, WM, WAL, WAN, WEE, WIT, WON, WYO, YATA, YF, YOG.
Hantaan virus was shown to be antigenically related to, but distinct from the recently registered Prospect Hill virus, rat isolates of Hantaan-like viruses and the agent of nephropathia epidemica [33] .

Section VI - Biologic Characteristics

Virus Source (all VERTEBRATE isolates)
Blood (M), blood (LV), lung (LV), kidneys (LV), parotid gland (LV), saliva (LV), urine (LV), and feces (LV)

Lab Methods of Virus Recovery (ALL ISOLATIONS)
Apodemus agarius coreae (weanling or adult), Apodemus agrarius jejuensis (weanling or adult); alveolar type II cells derived from human lung carcinoma (A-549)(4).

Cell system (a)	Virus passage history (b)	Evidence of Infection						
		CPE			PLAQUES			Growth Without CPE
		Day (c)	Extent (d)	Titer TCD50/ml (e)	Day (c)	Size (f)	Titer PFU/ml (e)	+/- (g)
A-549 (CL)	None	4-7	2+-4+	4-5 [a]				Sometimes
A-549 (CL)	Apodemus P1-P3	4-7	2+-4+	4-5				Sometimes
A-549 (CL)	Apodemus P5	10-14	0	2-4 [b]	Irregular	0-small	2-4 [a]	+
A-549 (CL)	A-549 P8	5-10	0	4-6 [b]	Irregular	0-small	4-6	+
WI-38 (CL)		5-10	0	4-6 [b]				+
MRC-5 (CL)		5-10	0	4-6 [b]				+
FRhL (CL)		5-10	0	4-6 [b]				+
FRhL (CL)	Apodemus P3	7-14	1+-3+	4-6 [b]				Sometimes
E6 (CL)	Various+ unpass.	>17	Irregular to none		6-8	1-4 mm	7.0	+ (24)

[a] Expressed in dex

[b] Fluorescent foci forming units/ml. Ultimate titer and day of peak titer are directly proportional to input multiplicity within the range of 0.0001 - 10.

NOTE: CPE is not a characteristic feature of infection with HTN virus and early reports of CPE may be attributed to contaminating viruses.

Section VII - Natural Host Range (Additional text can be added below table)

Vertebrate (species and organ) and arthropod	No. isolations/No. tested	No. with antibody/No. tested Test used	Country and region
Man (blood)	6/66	113/116 * IFA	South Korea; Seoul N. to 28 parallel (1)
Apodemus agrarius coreae (lung, kidney)	114/817		South Korea; along the Hantaan river near the 38th parallel; N.(1)
Apodemus agrarius jejuensis	0/238		
Microtus fortis pelliceus	0/103		
Crocidura lasiura	0/71		
Clethrionomys rufocanus regulus	0/35		
Cricetulus triton nestor	0/9		
Mus musculus yamashinai	0/17		
Tamias sibiricus asiaticus	0/1		
Man		7/542 IFA	North Greece (22), China (35, 40)
Suncus murinus (insectivore)	1/2		
Humans	7/1035 **		NC;CO, USA (39)
Humans		6/664 ** IFA	WV;MD, USA (39)

* Clinically severe cases. Inapparent infection rates, as indicated by significant levels of KHF antibody, range from 2.7% to 4% in long term residents of endemic areas to less than 1% in short term residents of endemic areas or long term residents of non-endemic areas.

** Patients with febrile illnesses of unknown origin (1035), or blood donors (664). Only 1 of 13 positive humans had both IFA and NT antibodies to Hantaan virus.

NOTE: It has not been established whether the Suncus murinus isolate is identical to Hantaan virus or to Seoul virus (prototype of rat isolates).

Section VIII - Susceptibility to Experimental Infection (include viremia)

Experimental host and age	Passage history and strain	Inoculation Route-Dose	Evidence of infection	AST (days)	Titer log10/ml

ICR Mice (nb)	Apodemus P-7	ic 0.025	Death	8-9	7.1
Mice (nb)	A549 P4; E6 P18	ip 0.03	Death		4.8
Mice (nb)	Strain76-118(41)	sc 0.025	Death		
Mice (wn)		ic 0.03	Irregular deaths		
Mice (wn)		ip			
Mice (ad)		im 0.3	No deaths, antibody prod.		
Mice (nb)		im,in 0.03	Death		5.0

Apodemus agrarius coreae, A. a. jejuensis and A. a. ningpoensis and 50% of Calomys callosus inoc im with various Apodemus (Ap) passage(P) levels of strain 76-118 develop FA detectable virus specific antigen in organs 18-21 days post inoc. Virus titers reach 7-8 log10/gram of lung tissue in Apodemus, and 2-4 log10 of virus in blood is demonstrable 7-10 days after inoculation (1,5).

Saimiri sciureus inoc im with Ap P-3 of Lee strain (human isolate) develop FA antibody and most inoc animals develop clinical signs of varying severity. Low level viremia is demonstrable 17-24 days after inoc (2).

Cercopithecus aethiops, Cebus apella, Callithrix jaccus, Maccaca mulatta, M. fasciculatus, S. sciureus, M. nemestrina, and Papio anubis inoc im with Ap P-5 76-118 or the 3rd A-549 TC passage of this virus, and Aotus trivirgatus inoc im with Ap P-3 Lee strain develop antibody with only occasional clinical signs or viremia (2,5).

Rattus norvegicus, Sprague-Dawley and Wistar strain white rats, strain 13 and Hartley guinea pigs, New Zealand white rabbits, A. peninsulae**** and A. speciosus**** (Japan) inoc im with Ap P-5 or P-7 76-118 virus develop antibody without clinical signs or detectable antigen in their organs (2,5). However, HTN virus infects Wistar Fisher rats after adaptation. Antigen detected 14-64 days pi. Circulating antibodies detected in sera of infected rats (21).

Gerbils (Meriones unguiculatus) newborns die after inoculation by ic or peripheral routes with Hantaan virus (36).

Wistar female Rattus norvegicus 12-16 wks. old, infected by inhalation (44).

**** Genus Apodemus

Section IX - Experimental Arthropod Infection and Transmission

Arthropod species & virus source(a)	Method of Infection log10/ml (b)		Incubation period (c)		Transmision by bite (d)		Assay of arthropod, log10/ml (e)		
	Feeding	Injected	Days	°C	Host	Ratio	Whole	Organ	System
Gamasid mites, Haemolaelaps glasgwi and Eulaelaps stabularis naturally infected by Hantaan virus; and virus could be transmitted by bite and transovarial transmission (41).									

Section X - Histopathology

Character of lesions (specify host)
Hemorrhagic lesions are found in the pituitary, the right atrium and the kidney. Edema in retroperitoneal tissues and mesentery. Intense capillary congestion and small areas of necrosis in the viscera (M).

Inclusion Bodies — Intranuclear

Organs/Tissues Affected
Heart: hemorrhage in the right atrium. Kidney: severe congestion of medulla. Pituitary gland: congestion and necrosis inanterior lobe. Lung: edema: (M) Virus grows in lung, kidney, liver,and parotid glands (LV).

Category of tropism
Kidney, parotid glands. (M) Lung, kidney and parotid glands (LV).

Section XI - Human Disease

In Nature
Significant

Residual
Significant

Death
Significant

Subclinical
Significant

Overt Disease
Significant

Clinical Manifestations
Fever, headache, vertigo, pharyngeal injection, nausea, rash, backache, proteinuria, hypostenuria, polyuria, hematuria, increased E.S.R., atypical lymphocytes, oligura, azotemia, constipation, hypotension, leukocytosis (>10,000/mm3), thrombocytopenia (<100,000/mm3).

Number of Cases
>10,000 (500-800/yr.)

Category (i.e. febrile illness, etc.)
Hemorrhagic fever with renal syndrome

Section XII - Geographic Distribution

Known (Virus detected)
Principally along the demilitarized zone (38th parallel-north) between North and South Korea, sporadically south-southwesterly beyond Seoul (1,6); and in China (38). Similar illnesses exist in Japan (7), Manchuria (8), USSR (9),

Suspected (Antibody only detected)
Antibody has benn found in animals and/or man worlwide.

Section XIII - References

1. LEE, H.W., et al. 1978. J. Infect. Dis., 137:298-308.
2. FRENCH, G.R. Unpublished observations.
3. SHOPE, R.E. Personal Communication. 1975.
4. FRENCH, G.R., et al. 1980. Science 211:1046-1048.
5. LEE, H.W., et al. 1980 Amer. J. Trop. Med. Hyg. 30:477-482.
6. SMADEL, J.E., et al. 1953. Am. J. Pub. Health 43:1327-1330.
7. TAMURA, M., et al. 1964. Biken J. 7:79-94.
8. ISHII, S., et al. 1942. Japanese Army Med. J. 355:1755-1758.
9. SMORODINTSEV, A.A., et al. 1944. Acad. Med. Sci. Moscow pp. 26-47.
10. GAJDUSEK, D.C. 1962. J. Pediatrics 60:851-857.
11. GAON, J., et al. 1968. Folia Medica Faculatatis Medicinae Universitatis Saraeviensis 3:24-41.
12. MYHRMAM, G., et al. 1951. Acta Med. Scand. 140:52-56.
13. LAHDEVIRTA, J., et al. 1971. Ann. Clin. Res. 3:12-17.
14. SVEDMYR, A., et al. 1979. Lancet i:100.
15. LEE, H.W., et al. 1979. Lancet i:186-187.
16. UMENAI, T., et al. 1979. Lancet i:1314-1316.
17. LEE, H.W., et al. 1979. Biken J. 22:41-44.
18. FRIMAN, G., et al. 1980. Lancet ii:100.
19. ASANAUMA, K. 1952. Misc. Rept. of Res. Inst. Nat. Resources(Tokyo)25:86-92.
20. ANONYMOUS. 1953. Dept. Army, TB Med. 240:1-23.
21. LEE, P.W., et al. 1981. Infect. Immun. 31:334-338.
22. LEE, H.W. and ANTONIADIS, A. 1981. Lancet i:832.
23. LEE, P.W., et al. 1981. Lancet ii:256-257.
24. McCORMICK, J.B, et al. 1982. Lancet i:765-768.
25. WHITE, J.D., et al. 1982. Lancet i:768-771.
26. DONNETS, M.A., et al. 1982. Lancet i:794-795.
27. GOLDGABER, D., et al. 1982. Lancet i:1184-1185.
28. HUNG, T., et al. 1983. Arch. Virol. 78:137-144.
29. SCHMALJOHN, C.S. and DALRYMPLE, J.M. 1983. Virology 131:482-491.
30. ELLIOTT, L.H., et al. 1984. J. Gen. Virol. 65:1285-1293.
31. SCHMALJOHN, C.S., et al. 1983. J. Inf. Dis. 148:1005-1012.
32. TSAI, T.F., et al. 1984. J. Inf. Dis. 152:126-136.
33. SCHMALJOHN, C.S., et al. 1985. Science 227:1041.
34. TSAI, T.F., et al. 1982. New Eng. J. Med. 307:623.
35. TANG, Y.W., et al. 1985. Lancet i:513-514.
36. ZHU, Z.Y., et al. 1984. Acta Microbiol. Sinica. 24:92-95.
37. KURATA, T., et al. 1983. Infect. Immun. 41:391-398.
38. JIANG, Y.T., et al. 1981. Chin. Med. J. 94:221-228.
39. YANAGIHARA, R., et al. 1985. Am. J. Trop. Med. Hyg. 34:396-399.
40. TANG, Y.W., et al. 1985. Lancet i:513-514.
41. Li, Faqing, et. al. 1986. Chin. J. Epidemiol. 7:200-202.
42. LEE, S.U. 1986. Korea Univ. Med. J. 23:73-80.
43. ANTONIADIS, A., et al. 1987. European J. Epidemiol. 3:295-301.
44. NUZUM, E.O., et al. 1988. Am. J. Trop. Med. Hyg. 38:636-640.

Remarks

Synonyms of human disease: Korean Hemorrhagic Fever, Epidemic Hemorrhagic Fever, Songo Fever, serologically related and clinically similar diseases are referred to as Hemorrhagic Fever with Renal Syndrome, Hemorrhagic Nephroso-Nephritis, and Nephropathia Epidemica. Experiments designed to demonstrate transmission of the virus by mites have been equivocal (1, 19, 20).