

**Virus Name: Dengue 4**

**Abbreviation: DENV**

**Status:** Arbovirus

**Select Agent:**

**SALS Level:** 2

**SALS Basis:** S

**HEPA Filtration:**

**Antigenic Group:** B

**Taxonomic status:** *Flavivirus*

**Other Information:** Department of Commerce permit required.

**Section I - Full Virus Name and Prototype Number**

**Full Virus Name:**

**Prototype Number:**

Dengue 4

H-241 (1,2)

**Information from:** W.McD. Hammon

**Date:**

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1/27/1985

**Address:** Grad. Schl. of Public Health, Univ. of Pittsburgh, Pittsburgh, PA 15213

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Reviewed by editor

**Section II - Original Source**

**Isolated by:** G. Sather and W.McD. Hammon **at:** Grad. Schl. of Public Health, Univ. of Pittsburgh, Pittsburgh, PA 15213

**Genus and species:** Man

**Sentinel** X

**Age/Stage:** 10 years **Sex:** F

Isolated From	Isolation detail
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**Signs and symptoms of illness:** Sudden onset, fever, headache, muscle and joint pain, rash\*

**Arthropod engorged** depleted gravid

**Time held alive before inoculation:**

**Collection date:** 8/28/1956 **Method:** Venipuncture

**Place collected:** San Lazaro Hospital, Manila

**Latitude:** 14° 35' " N

**Longitude:** 121° ' " E

**Macrohabitat:** Quezon City, Manila, Philippines

**Microhabitat:**

**Method of storage until inoculated:** Dry ice, then Revco freezer at -55dC or lower

**Footnotes:**

**Section III - Method of Isolation and Validity**

**Inoculation Date:** 4/15/1957

**Animal:** nb mice

**Embryonated egg:**

**Tissue Culture:**

(Details in Section VI - Biologic Char.)

**Route inoculated:** Intracerebral

**Reisolation:** Yes

**Other reasons:** Subsequent isolations from other patients with antibody rise.

**Homologous antibody formation by source animal (See Section II):** Not tested

**Test used:** HI

CF

NT

**Other:**

**Footnotes:**

Section IV - Virus Properties

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Physicochemical:

RNA:	DNA:	Single Strand:	Double Strand:
Pieces:	Infectivity:	Sedimentation coefficient(s):	</strong>
Percentage wt. of virion protein		, lipid	carbohydrate
Virion polypeptides:			
Number:	Details:		
Non-virion polypeptides:			
Number:	Details:		
Virion density:		Sedimentation coefficient:	
Nucleocapsid density		Sedimentation coefficient:	

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Stability of infectivity (effects) pH

Lipid solvent:		
(ether)	After treatment titer	Control titer
(chloroform)	After treatment titer	Control titer
Detergent:		
(deoxycholate) 1:1000	After treatment titer <2.0 dex	Control titer 6.5 dex (5)
Other (formalin, radiation):	Probably similar to types 1 and 2.	

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Virion morphology:

Shape	Spherical	Dimensions	45-50 nm
Mean (nm)	range (nm)	how measured	EM thin-sections of LLC-MK2 cells (3)
Surface projections, envelope	Envelope spikes present; spherical incrystalline f		
Nucleocapsid dimensions, symmetry	Core size - 25-28 nm (4)		

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Morphogenesis:

Site of constituent formation in cell	
Site of virion assembly	Membranes of endoplasmic reticulum
Inclusion bodies	
Other	

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Hemagglutination:

Hemagglutination	Yes	Antigen source	SMB ext. by sucrose-acetone		
Erthrocytes	Goose	pH range	6.4-7.4	pH optimum	7.0
Temperature optimum	24dC (5)	range	24dC and 37dC.		
Remarks	See DEN 1 and 2 for HA and CF antigen fractions. * Seen during epidemic of Philippine hemorrhagic fever (incomplete clinical record).				
Serologic methods recommended	PRNT, immunodiffusion, CF, HI				
Footnotes:	See DEN 1 and 2 for HA and CF antigen fractions. * Seen during epidemic of Philippine hemorrhagic fever (incomplete clinical record).				

## Section V - Antigenic Relationship And Lack of Relationship To Other Viruses

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See DEN 1 and 2 for general antigenic relationships with other Group B viruses and dengue viruses.

Type 4 had the same early association with hemorrhagic fever as type 3, having been isolated first during an epidemic of Philippine hemorrhagic fever. Subsequent isolations elsewhere during epidemics without hemorrhagic fever cases places it in the same position as the other three types - found both in hemorrhagic fever patients and epidemics and in classical dengue fever patients and epidemics.

**Section VI - Biologic Characteristics**

**Virus source (all VERTEBRATE isolates):** Blood (M), liver (M)

**Lab Methods of Virus Recovery (ALL ISOLATIONS):** Newborn mice; LLC-MK2 and mosquito cell cultures; inoculation of adult mosquitoes.

**Susceptibility of Cell Culture Systems:**

Cell system (a)	Virus passage history (b)	Evidence of Infection							Growth Without CPE +/- (g)
		CPE			PLAQUES				
		Day (c)	Extent (d)	Titer TCD50/ml (e)	Day (c)	Size (f)	Titer PFU/ml (e)		
Forms plaques in Vero and and LLC-MK2 (CL)(15); RMK (PC) and PS-Y-15 (CL) (16); MA-104 (CL) and MA-111 (CL) (17); forms plaques and produces CPE in PS (CL) (18); produces CPE in BHK-21 (CL) (19); multiplies and/or produces CPE in C6/36 (CL) Aedes albopictus (CL) (20) and AP-61 (CL) (21,22). Forms plaques in Aedes albopictus (23).									

**Section VII - Natural Host Range**

Vertebrate (species and organ) and arthropod	No. isolations/No. tested	No. with antibody/No. tested Test used	Country and region
Man *	Many		SE Asia(1,2), India(6), Philippine Is. (1,2), Indonesia, New Guinea
Aedes aegypti	Many		SE Asia, Philippine Is., India (7)
* Numerous isolations from acute phase blood, days 1-5. Principal source of mosquito infection.			
Note: Aedes niveus and Anopheles (Cel) balabacensis introlatus most likely jungle canopy vectors for dengue in Gunong Besout Forest, Malaysia (25).			

**Section VIII - Susceptibility To Experimental Infection (Record Viremia)**

Experimental host and age	Passage history and strain	Inoculation Route- Dose	Evidence of infection	AST (days)	Titer log10/ml
Mice (nb)	P >21	ic 0.01	Death	3	7.0-8.5
Mice (nb)		ip 0.03	Death	10-17	<1.0
Mice (nb)		sc			
Mice (wn)		ic 0.03	Death	8-20	7.5
Mice (wn)		ip 0.1	None		
hamster (ad)	P >21	ic 0.1	None		
guinea pig (yg)		ic 0.1	None		
rabbit (yg)		ic	None		
monkey (yg)	P 21	ic	NT antibody only		
(yg)	P >21	sc, intracut	NT antibody only		

## Section IX - Experimental Arthropod Infection And Transmission

Arthropod species & virus source(a)	Method of Infection log10/ml (b)		Incubation period (c)		Transmission by bite (d)		Assay of arthropod, log10/ml (e)		
	Feeding	Injected	Days	°C	Host	Ratio	Whole	Organ	System
Parenteral passage in <i>Aedes albopictus</i> demonstrated.									
Cannot be passed in <i>Blattella germanica</i> , <i>Cimex lectularis</i> , <i>Attageus piceus</i> , <i>Plodia interpunctella</i> , <i>Culex tritaeniorhynchus</i> , or <i>Ornithodoros savignyi</i> (8).									
<i>Aedes aegypti</i> readily infected by intrathoracic inoculation or feeding on viremic mice (10).									
Natural transovarial transmission of DEN-4 virus in <i>Aedes aegypti</i> (26).									

## Section X - Histopathology

**Character of lesions:** In man: (See DEN-1). sm: varying degrees of neuronolysis, and chromatolysis. Lesions generally more severe in cerebral cortex. Vascular endothelium changes noted. No prominent perivascular infiltration (9).

**Inclusion bodies:**

**Cytoplasmic:**(M) (LV) **Intranuclear:** (M) (LV)

**Organs-tissues affected:** Brain (LV), spinal cord (LV), lungs (M), liver (M), heart (M), blood vessels (M), marrow (M); no consistent lesions noted in viscera of suckling mice.

**Category of tropism:** Neurotropic in mouse

## Section XI - Human Disease

<b>Human disease:</b>	<b>In nature:</b>	(S) X
	<b>Death:</b>	(S) X
	<b>Residua:</b>	(S) (R)
<b>Laboratory infections:</b>	<b>Subclinical:</b>	(S) (R)
	<b>Overt Disease:</b>	(S) (R)

**Clinical manifestations:** Fever, headache, prostration, myalgia, arthralgia, CNS signs (including encephalitis), hemorrhagic signs, leukopenia, rash, lymphadenopathy, vomiting; abdominal pain, shock, thrombocytopenia, petechiae, positive tourniquet test in hemorrhagic fever of SE Asia

**Category:** Febrile illness with rash, hemorrhagic fever

**No. of cases:** Many; classical dengue fever and hemorrhagic fever

## Section XII - Geographic Distribution

**Known (virus):**

Essentially all countries of SE Asia; incl. Philippine Islands; Sri-Lanka; India, Rep. of China, S. Pacific, Cent. America, Surinam, Mexico, Colombia, Venezuela, Brazil, Caribbean, Guatemala, Honduras, W. Africa

## Section XIII - References

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**Section XIV - Remarks**

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Two recent series of articles relating to extensive studies made in Bangkok, Thailand after 1962 on dengue hemorrhagic fever by Halstead, S.B., et al. will be found in 1969, *Amer. J. Trop. Med. Hyg.* 18:954-1033, and 1970, *Yale J. Biol. Med.* 42:261-362. See also following Seminars: Symposium on Hemorrhagic Fever, SEATO Medical Res. Mono. No. 2, Bangkok, 1961, WHO Seminar on Mosquito-borne Hemorrhagic Fevers in the South-east Asia and Western Pacific Regions, Bangkok, 1964. Reports on the Second Regional Seminar on Virus Diseases; Mosquito-borne Virus Diseases, WHO Regional Office for the Western Pacific, Manila, 1969.