work in progress. Serotonin or histamine antagonists do not interfere with the measurable inhibition of Sarcoma 180 or Ehrlich Ascites in mice, induced by HN_2. The antagonists afforded a measure of protection for the HN_2-treated tumor-bearing mice, similar to that reported here.

Summary. Intraperitoneal administration of either of 2 anti-histamine compounds before and after a single intraperitoneal nearly-lethal dose of nitrogen mustard had been given to mice produced a marked reduction of the mortality expected from the nitrogen mustard. The leukopenia resulting from the nitrogen mustard in combination with the anti-histamines was less in extent and duration.

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Assay of Mouse Adapted Dengue Viruses in Mammalian Cell Cultures by An Interference Method. (29117)

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Several authors have reported growth of dengue viruses in mammalian cell cultures with and without cytopathic effect(1-9). As yet, however, no *in vitro* system has been shown to be as sensitive as the suckling mouse for assay of all available dengue serotypes. Recent application of viral interference in tissue culture to the study or isolation of common cold(10), rubella(11) and several arthropod-borne viruses(12-15) stimulated a search for an analogous system for dengue viruses. This paper reports the successful use of an interference test to demonstrate the susceptibility of several primary and stable mammalian cell cultures to mouse adapted dengue virus types 1-4, and to 2 new dengue prototypes, TH-36 and TH-Sman, recovered from hemorrhagic fever patients in Thailand (16).

Materials and methods. Viruses. The following viruses were employed: dengue type 1, Hawaiian strain, 70th mouse passage; dengue type 2, Trinidad 1751 strain, 68th mouse passage; dengue type 3, strain H-87, 35th mouse passage; dengue type 4, strain H-241, 35th mouse passage; TH-36 (tentatively designated as dengue type 5 by Hammon)(16), 15th mouse passage; TH-Sman (tentatively designated as dengue type 6 by Hammon) (16), 15th mouse passage; chickungunya, Ross strain, 175th mouse passage; Coxsackie B1, strain unknown, multiple monkey kidney cell and 10 hamster kidney cell passages and polio type 1, strain unknown, with more than 50 monkey kidney cell passages. Dengue viruses were received from Dr. W. McD. Hammon, chickungunya from the Rockefeller Foundation Virus Laboratory and enteroviruses from the Virus Department, Walter Reed Army Institute of Research.

Cell cultures. Continuous cell cultures employed were as follows: grivet monkey kidney, BS-C-1(17), received in December 1962 from Microbiological Associates, Bethesda, Maryland via Walter Reed Army Institute of Research; rhesus monkey kidney, LLC MK2, series 2(18), received April 1963 from Dr. Robert Hull, Biological Research Division, Eli Lilly, Indianapolis, Ind.; porcine kidney cells, PS(19), received November 1962 from Dr. Y. Kanda Inoue, Virus Research Inst., Kyoto, Japan; and a Microbiological Associates strain of HeLa supplied December 1961 by Lt. Cdr. Irving Green, NAMRU-2, Taipei, Taiwan.

Trypsinized monolayers used were monkey

TABLE I. Tissue Culture Growth and Maintenance Media Used in Dengue Virus Studies.

Primary or stable cells	Basic media: B.S.S. or medium	Growth and maintenance: Lactalbumin hydrolysate‡	Growth and maintenance: Tryptose phosphate broth‡	Growth and maintenance: Glutamine‡	Growth only: Yeastolate‡	Sera: Growth	Sera: Maintenance
		(%)	(%)	(%)	(%)		
HKC	Hanks'	.5	15	—	—	8% calf*	3% new born calf†
MKC	"	.5	15	—	—	4% "	2% calf*
PS	Earle's	.5	—	—	.1	10% "	2-3% "
MK 2	M-199	—	—	.05	.1	20% "	5% new born calf†
BS-C-1	"	—	—	.05	.1	20% fetal calf†	5% new born calf†
HeLa	Eagle's	—	—	—	—	10% calf*	2-4% calf*

* Dengue antibody free calf serum obtained in Thailand. Heat inactivated at 56°C for 30 min.
† Microbiological Associates.
‡ Difco Laboratories, Detroit, Mich.

kidney cells, MKC, prepared from Thailand *Macaca irus* by the method of Bodian(20) and hamster kidney cells, HKC, prepared by the method of Diercks(21). Growth and maintenance media used for cell cultures are shown in Table I. All media contained 500 units of penicillin and 500 μg of streptomycin per ml.

Mice. One- or two-day-old mice used were from a colony of Swiss albinos originally derived from the Rockefeller Foundation Virus Laboratory Webster strain and sent to Thailand from the Virus Research Centre, Poona, India.

Inoculation of tissue cultures and mice. Two ampules containing 20% virus-mouse brain suspension were pooled for each dengue virus titration. Ten-fold dilutions were made in the maintenance medium of the cell culture being inoculated. Two litters of 8 suckling mice were inoculated intracerebrally (IC) with 0.02 ml, and 3 or 4 tissue culture tubes were inoculated with 0.1 ml of each virus dilution. Growth medium was poured off the cell sheet just prior to inoculation of tubes with virus dilutions. Inoculated tubes were incubated in a slanted position for 2 hours at 34°C; then 1.0 ml of maintenance medium was added. Tubes were incubated at 34°C; media changes were made every 5 days and pH was adjusted at frequent intervals to pH 7.2-7.4 with 4.0% sodium bicarbonate. Cells were examined daily for cytopathic effect (CPE). Mice were observed for sickness or death for 21 days and LD_{50} was calculated by the method of Reed and Muench(22).

Challenge virus resistance (CVR) test. To detect presence of dengue virus in cell cultures, 2 tubes of each dilution not showing CPE on the 8th post-inoculation day were challenged with approximately 100 TCD_{50} of a second virus producing rapid CPE. Challenge virus inocula (0.1 ml) were added directly to maintenance medium. Challenged tubes were incubated at 37°C. The challenge virus for MKC, MK2 and BS-C-1 was polio type 1; for HKC and PS cells, respectively, chikungunya and Coxsackie B1 viruses were used. Each test contained one or two tubes at each dengue virus dilution which were unchallenged and observed for 16 days for direct dengue induced CPE. For each lot of cells additional controls were added. These were, 1) normal cell control, 2) challenge virus control (comprised of 4 or more uninfected tubes inoculated at the same time and with the same amount of challenge virus as used in dengue virus titrations) and 3) challenge virus titration. Dengue virus inoculated tubes showing 0-1 + CPE 24 hours *after* challenge virus control tubes showed 4+ CPE were considered to be CVR positive (CVR+).

TABLE II. Maximal Titers of Mouse Adapted Dengue Viruses Observed in Tissue Cultures and Suckling Mice.

Dengue virus type	Mouse passage	Suckling mouse virus titers neg $\log_{10}$ (LD_{50}/0.1 ml)	Tissue culture virus titers neg $\log_{10}$ InD_{50}/0.1 ml					
			MKC	HKC	HeLa	MK 2	PS	BS-C-1
1	70	6.7	0/5.2*	0	0	6.5	3.5	7.5
2	68	7.3	3.5/6.4*	5.5	0	6.2†	7.5†	8.5
3	35	6.7	3.5/6.5*	5.2	0	4.5	3.5	6.5
4	35	7.3	3.5/7.8*	0	0	6.5	2.5	7.5
TH-36	15	8.0	ND	6.5	0	6.5†	7.5†	8.5
TH-Sman	15	6.3	ND	4.5	0	6.0	4.0	7.0

* Figures in denominator denotes suckling mouse titer of dengue virus one mouse passage lower than shown in column 2.
† TCD_{50} based upon direct CPE.

Dengue virus titers (expressed as InD_{50}) were calculated by the method of Reed and Muench(22) from the occurrence of CVR+ tubes.

Results. Development of interference. In preliminary experiments conducted in 1961 the growth of dengue virus type 3 and development of challenge virus resistance in infected primary monkey kidney cells was studied at incubation temperatures of 34°C, 37°C and 39°C and at an average pH of 6.8, 7.2 and 7.6. While growth of dengue 3 virus, as determined by titration in suckling mice, was optimal at 37°C and pH 7.6 titers obtained by CVR technique were 5-20-fold higher at 34°C and pH 7.2 than at other temperatures or pH. The time of development of interference was observed to be related to the number of infectious doses of dengue virus inoculated. Thus, following the inoculation of 100,000 suckling mouse LD_{50} of dengue 3 interference could be demonstrated by virus challenge 3 days after infection, while inoculation of 1-10 LD_{50} produced detectable interference no earlier than the 8th or 10th day. The size of challenge virus dose was also related to the development of interference. With 10,000 TCD_{50} of polio virus type 1 interference could be demonstrated only after 10 to 15 days of primary incubation and dengue virus assay results were frequently 10-100-fold lower than when 10-100 TCD_{50} were used. Although 1-10 TCD_{50} of challenge virus resulted in earlier and a more complete interference effect, CPE appearance was often delayed and unreliable. The conditions found to be optimal for demonstration of dengue 3-poliovirus interference were applied to the remainder of the cell lines and viruses screened.

Dengue assay. Maximal CVR titers observed for the mouse adapted dengue viruses and cell cultures employed are shown in Table II. Replicate titrations performed in several cell lines at various intervals over a 12-month period are shown in Table III. Titrations were made using the same lot of virus but were often performed by different individuals. It seems unlikely that the variations in titer observed most frequently in HKC and MK2 cells were caused by diluting errors since replicate check titrations of challenge viruses (Table IV), performed at the same time by the same technicians, were remarkably consistent. Complete or partial dengue virus CPE resembling polio virus CPE was observed in some instances and may occasionally have been responsible for misinterpretation of end points in the CVR test. On several occasions direct dengue 2 and TH-Sman CPE were observed in BS-C-1 and MK2 tubes, respectively, containing 10^{-1} to 10^{-3} dilutions, while tubes inoculated with higher dilutions up to 10^{-5} or 10^{-6} failed to show CPE but were resistant to polio virus challenge.

Of the cell lines tested only BS-C-1 cells gave titration results with all dengue strains which were equal to or better than results obtained by intracerebral inoculation of suckling mice. MK2 cells were nearly as satisfactory; however, titers of dengue virus type 3 and TH-Sman were consistently below BS-

TABLE III. Replicate Titrations of Indicated Lots of Dengue Virus in Cell Cultures.

Dengue virus	Mouse passage	Suckling mouse virus titers neg $\log_{10}$ LD_{50}/0.1 ml	Tissue culture virus titers neg $\log_{10}$ InD_{50}/0.1 ml HKC	MK 2	BS-C-1
1	70	6.3, 6.7	0, 0	4.5, 6.5, 6.5	4.5, 6.5, 7.5, 7.5, 7.5
2	68	7.0, 7.3	4.5, 5.5, 5.5	6.2*, 3.5*, 5.5*	(3.5*, 6.5), 8.5, 8.5, 7.5
3	35	6.7, 6.5	4.5, 5.2, 3.0	4.5, 3.5, 3.5	6.0, 6.5, 7.0, 6.5, 6.5
4	35	6.7, 7.3	0, 0	3.5, 6.5, 6.0	5.5, 7.5, 7.5, 7.5
TH-36	15	7.5, 8.0	6.5, 6.5, 6.5	6.5*, 6.5*, 5.5*	6.0, 7.5, 8.0, 8.5, 8.0
TH-Sman	15	6.3, 5.9	2.5, 4.5, 4.0	(5.5, 3.5*), (6.0, 3.5*), 4.0	6.5, 7.0, 6.5, 6.0, 5.5

* CPE before 8 days. ( ) Same experiment.

TABLE IV. Reproducibility of Challenge Virus Titrations in Several Cell Lines.

Virus	Cell culture	Virus titers neg $\log_{10}$/0.1 ml	Dilution virus inoculum	Day 4 + CPE observed
Chikungunya	HKC	6.5, 6.7, 7.0, 7.0, 7.0, 7.0, 7.0, 6.5, 6.5	$10^{-4.5}$	3
Coxsackie B 1	PS	7.5, 6.5, 6.5, 6.5, 6.5	$10^{-4.5}$	4 ± 1
Polio 1	BS-C-1	5.0, 5.2, 5.0, 5.2, 5.2, 5.5, 5.2, 4.0, 5.0, 5.7	$10^{-3.0}$	6 ± 1
" 1	MK 2	5.5, 5.6, 5.5, 5.5, 6.2	$10^{-3.5}$	6 ± 1

C-1 and suckling mouse titers. Complete destruction of MK2 cells was observed 5-8 days following inoculation of dengue type 2 and strain TH-36. PS cells were equally as susceptible to the cytopathic effects of dengue type 2 and TH-36, but not as sensitive in the CVR test as BS-C-1 or suckling mice for dengue types 1, 3, 4 and TH-Sman. In HKC, no interference was observed with dengue types 1 and 4 and low titers were obtained with other types except dengue type 5. No interference to polio virus could be demonstrated in MKC infected with dengue type 1 and dengue types 2, 3 and 4 showed low interference titers. In contrast to the observations of Hotta and Evans(1,2) CPE was not noted in primary MK cells infected with either dengue 1 or 2. However, cells in our studies were not observed after 16 days' incubation. The strain of HeLa cells tested gave completely negative results in the CVR test.

To determine whether BS-C-1 cells became resistant to challenge virus when infected with very small doses of dengue virus, undiluted tissue culture fluid from unchallenged tubes at limit dilutions of all 6 dengue virus types were inoculated IC into suckling mice. Tubes had been inoculated with dengue virus dilutions 14 days earlier. Presence or absence of mouse pathogenic dengue virus recovered at terminal dilutions in BS-C-1 tubes corresponded with one exception with results obtained by CVR test of challenged companion tubes (Table V).

Neutralization test. Using BS-C-1 cells as

assay system, virus neutralization tests have been readily accomplished in tissue culture. Neutralization of dengue 1 by homologous mouse hyperimmune serum shown in Table VI illustrates results and methodology of tissue culture neutralization test. As recommended by Sabin(23) unheated, fresh, antibody-free rabbit serum was added to mouse hyperimmune serum as "accessory factor" for suckling mouse tests. "Accessory factor" was not added to antiserum in tissue culture tests. It should be stressed in performing

TABLE V. Correlation of Challenge Virus Resistance and Presence of Dengue Virus at Terminal Virus Titrations in BS-C-1 Cells.

Dengue virus type	Test system	Results in tubes inoculated with indicated virus dilutions					
		10^{-7}		10^{-8}		10^{-9}	
1	CVR	+	+*	0	0	0	0
	SM	ND	ND	0/16†	16/16	0/16	0/16
2	CVR	+	+	+	+	0	0
	SM	ND	ND	ND	ND	0/16	0/16
3	CVR	+	+	+	0	0	0
	SM	ND	ND	16/16	0/16	0/16	0/16
4	CVR	+	+	0	0		
	SM	ND	ND	0/16	0/16		
TH-36	CVR	+	+	+	0	0	0
	SM	ND	ND	16/16	0/16	0/16	0/16
TH-Sman	CVR	+	+	0	0		
	SM	ND	ND	0/16	0/16		

+ CVR positive. 0 CVR negative. ND Not tested.

* Tubes challenged with 100 TCD_{50} of type 1 polio 8 days after inoculation of indicated dilution of dengue virus.

† Undiluted TC fluid inoculated IC in suckling mice 14 days after inoculation of cells with indicated dilution of dengue virus. Mice dying within 21 days are shown in numerator; total mice inoculated are shown in denominator.

TABLE VI. Neutralization Test in BS-C-1 Cells of Dengue 1 Virus with Homologous Hyperimmune Mouse Serum. Results at day 14 reading are shown.

Specimen	Tubes	CPE observed at indicated final dengue virus dilution 6 days after inoculation with 0.1 ml of 10^{-3} dilution polio 1					Interpretation
		10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	
Normal mouse serum (1:10 dil)* + dengue 1	1	0‡	0	0	0	4+	$InD_{50} = 10^{7.5}$
	2	0	0	0	0	3+	
	Control†	0	0	0	0	0	
	"	0	0	0	0	0	
Dengue 1 immune serum (1:10 dil)*§ + dengue 1	1	0	4+	4+	4+	4+	$InD_{50} = 10^{4.5}$ (LNI = 3.0)
	2	0	4+	4+	4+	4+	
	Control†	0	0	0	0	0	
	"	0	0	0	0	0	

		Polio virus type 1 check titration				
		10^{-3}	10^{-4}	10^{-5}	10^{-6}	
Polio 1	1	4+	4+	3+	0	$TCD_{50} = 10^{5.3}$
	2	4+	3+	2+	0	
	3	4+	4+	1+	0	
	4	4+	2+	0	0	

* Equal parts of virus dilution and heat-inactivated serum mixed and incubated at 37°C for 2 hours prior to inoculation of tubes.

† No polio virus added to tubes.

‡ 0 = No CPE, 1 = 25%, 2+ = 50%, 3+ = 75%, 4+ = 100% of cell sheet showing cytopathic effect.

§ LNI in suckling mice = 3.5 (virus diluted in fresh nonheat-inactivated antibody-free rabbit serum).

neutralization tests with the CVR technique that at each dilution 1 or 2 dengue virus-serum tubes should not be challenged but observed for the appearance of direct dengue virus CPE.

Discussion. From data presented it is evident that the phenomenon of viral interference in cells infected with dengue virus occurs in a variety of mammalian cells. Of the cell studied and with methods employed, BS-C-1 cells have the broadest spectrum of susceptibility to all dengue serotypes and give virus assay results as good as, or better than, those recorded for the suckling mouse. There is evidence that infection in this highly susceptible cell is initiated by very few virus particles and that such minimal primary infections result in detectable interference to a challenge virus. This was demonstrated by the consistently high titers of dengue virus *vis a vis* mouse titers measured by the CVR technique and by the close correspondence of dengue virus recovery in mice and CVR positive tubes at the limit of virus titrations.

Test conditions were adopted from studies of the growth of dengue type 3 virus in primary monkey kidney cells. These experiments suggested that the sensitivity of virus assay was inversely related to challenge virus dose and directly related to the length of incubation of dengue virus in cells prior to challenge. Selection of 100 TCD_{50} as challenge virus dose and the 8th day for challenge were made so that CPE would occur reliably and would be complete on the 14th-16th day, or before spontaneous degenerative changes were noted in cell monolayers. Using the methods described, several laboratory workers have encountered no difficulties over a period of 12 months in obtaining reproducible dengue virus titration in BS-C-1 cells within the limits of accuracy generally accepted for assay of viruses in fluid overlay cell cultures. Other cell lines tested were not as reliable or as susceptible as the suckling mouse to all dengue virus types. Such results may reflect variations in the proportion of tissue culture virulent virus in populations of mouse adapted dengue viruses. The observation that many dengue viruses did produce some evidence of challenge virus resistance in tested cell cultures suggests, however, that results may be improved by determination of factors critical for sensitivity and reproducibility of dengue virus assay for each virus and cell system.

The broad spectrum sensitivity of BS-C-1 cells to all known dengue virus types provides for the first time a highly sensitive *in vitro* alternate to the suckling mouse for the study of mouse adapted dengue viruses. In addition, BS-C-1 cells satisfy other criteria of utility. During 12 months' study these cells have maintained uniform growth characteristics and viral susceptibilities. Preliminary experiments in our laboratory have shown that serum neutralization tests and identification of newly isolated mouse adapted dengue viruses are readily accomplished by use of the BS-C-1 cell interference test. The use of fetal calf serum in outgrowth medium instead of human serum as used in the dengue sensitive HeLa cell system(8) avoids the danger of introducing dengue antibodies in a dengue virus assay. Further observations are in progress to determine the sensitivity of this cell system to dengue viruses of human and arthropod origin.

Summary. Using a viral interference test BS-C-1 cells (a stable grivet monkey kidney line) were found to be as sensitive as the suckling mouse for the assay of mouse adapted prototype strains of all available serotypes of dengue virus. Two other stable cell lines PS (pig kidney) and LLC MK 2 (stable rhesus kidney), while not as susceptible to all dengue serotypes as BS-C-1, showed CPE to dengue 2 and TH-36. Two primary cell cultures, MKC and HKC, were not susceptible to all dengue viruses, while a strain of HeLa cells gave no evidence of development of interference following inoculation of dengue viruses. Applications of the tissue culture interference test are discussed.

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5-Hydroxytryptamine in the Gastrointestinal Tract After Intestinal Obstruction or Hepatectomy. (29118)

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5-Hydroxytryptamine occurs in the gastrointestinal mucosa of the dog in concentrations of 7 to 14 μg/g with the pyloric region containing the highest concentration(1). In the rabbit, 5-hydroxytryptamine has a half-life of 10 and 17 hours in the mucosa of the stomach and intestine, respectively(2). Such a rapid turnover of considerable quantities of 5-hydroxytryptamine has suggested that it may have an important function in the gastrointestinal tract, possibly in regulation of motility(3,4). 5-Hydroxytryptamine has been found to have a very potent action on the motility of the gastrointestinal tract(5) and methods for assay of this substance are dependent on the extreme sensitivity of the ileum of guinea pig and colon of rat to nanogram quantities(1,6). Hypermotility of the gastrointestinal tract accompanied by reversed peristalsis occurs proximal to an intestinal obstruction and also is present after hepatectomy and in intoxicated Eck's-fistula dogs.

Rosenberg and his colleagues(7) reported that no changes occurred in the amounts of 5-hydroxyindoleacetic acid in urine or of 5-hydroxytryptamine in plasma in 7 dogs after simple intestinal obstruction; measurements were not made of the concentration of 5-hydroxytryptamine in the gastrointestinal mucosa. Sigel and co-workers(8) found that urinary excretion of 5-hydroxyindoleacetic acid did not change from normal in 6 dogs after ligation of the arterial supply to the mesenteric small bowel and strangulation of the middle 2 feet of the small intestine with cord. The purpose of the present investigation was to compare the concentration of 5-hydroxytryptamine in the gastrointestinal mucosa of dogs after hepatectomy or intestinal obstruction with that in dogs after laparotomy. Measurements also have been made of concentrations of 5-hydroxytryptamine in blood and in brain and of 5-hydroxyindoleacetic acid in urine.

Methods and materials. Dogs weighed from 7 to 15 kg. All bowel obstructions were made in the jejunum about 12 inches from the