

CLINICAL OBSERVATIONS ON DENGUE HEMORRHAGIC FEVER IN THAILAND

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ABSTRACT

Sixty confirmed dengue virus infections and three chikungunya virus infections in children in Thailand were studied clinically by a single observer. A majority of 52 hospitalized dengue infected patients had a distinct and recognizable syndrome characterized by a first phase non-descript febrile illness of 2 or more days duration, followed by hepatomegaly and positive tourniquet test or other evidence of hemostatic abnormality. Fifteen patients developed shock and/or coma and 3 died. Shock was accompanied by loss of fluid into serosal cavities and decreased blood volume. Chikungunya patients did not manifest shock. The dengue hemorrhagic fever syndrome differs markedly from classical dengue fever. The reason for the prevalence of this variant dengue virus syndrome in Southeast Asia is not known.

Since 1955 a fatal epidemic disease of children characterized by fever, hepatomegaly, shock and bleeding phenomena has been described in nearly every country in Southeast Asia (1). At least 4 distinct types of dengue virus have been associated with disease outbreaks and Aedes aegypti has been established as the urban vector. Recently, Gadjusek has proposed the name dengue hemorrhagic fever, one of the mosquito-borne hemorrhagic fevers, to designate these outbreaks (2). This disease has been also referred to as Southeast Asian hemorrhagic fever (3), Thai (4), Philippine (5), and Singapore hemorrhagic fever (6).

Several descriptions of hemorrhagic fever in Thailand have been written: the early and generally accurate report of Nelson (7); the comparative descriptions of Philippine and Thai hemorrhagic fever by Hammon and associates (8) and the detailed analyses of large series from major Thai hospitals published in the SEATO Medical Research symposium on Thai hemorrhagic fever (9). None of these reported series has been based upon data obtained during a prospective study with standardized clinical examination of virologically studied patients.

The present study attempts to define the severe, moderate and mild syndrome associated with proven dengue virus infection in Asian children in Thailand seen in 1962. Limited observations on infection with chikungunya virus, an agent repeatedly associated with outbreaks of hemorrhagic fever, are also included.

Materials and Methods. Selection and study of patients. The study was conducted at Children's Hospital, Bangkok, during a period of seven weeks during August and September 1962. Patients were seen in the out-patient department, or on the surgical or medical wards following their disposition by the staff of Children's Hospital. Clinical examination for this study did not substitute for or alter in any way the evaluation undertaken by staff physicians. Management of patients was under the supervision of the second author (SN). Patients who were residents of Bangkok or Thonburi were admitted to study on Mondays, Wednesdays and Fridays. On each day five patients from four categories were studied; (1) (HFI) Two patients admitted to hospital with a diagnosis of hemorrhagic fever; (2) (NH) One patient admitted to hospital with any febrile (100° F or higher) disease other than hemorrhagic fever; (3) (S) One patient admitted to the surgical service; and (4) (PUO) One patient with a fever of 100° F or higher seen in the out-patient department and not admitted to the hospital.

Clinical and laboratory examinations of all patients were similar. On admission a medical history was elicited with the aid of a bilingual assistant and a complete physical examination was accomplished and recorded. Each HFI and NH patient was examined daily until discharge, surgical patients were observed daily for 1 week and PUO patients were observed for 1 to 3 days. All admission and subsequent observations were made by a single observer (MRM). Ninety-four patients were studied, 63 of whom had unequivocal evidence of a current dengue or chikungunya virus infection (Table 1). Of 60 confirmed dengue virus infections, 51 were diagnosed clinically as hemorrhagic fever, 8 had a milder illness not requiring hospitalization and 1 patient was hospitalized with a diagnosis of fever

Table I

CLINICAL DIAGNOSES AND ETIOLOGY OF 94 IN-AND OUT-PATIENT EXAMINED
AT CHILDREN'S HOSPITAL, BANGKOK, 1962

ETIOLOGY

Clinical diagnosis	Total studied	DENGUE			CHIKUNGUNYA				No. virus diagnosis
		Total con-firmed	Virus isol.	Diagnostic titer rise	High fixed titer *	Total con-firmed	Virus isol.	Diagnostic titer rise	
Hemorrhagic fever in-patient	56	51	4	36	15	2	2	2	3
Misc. febrile disease in-patient	11	1	0	1	0	0			10
Misc. febrile disease out-patient	15	8	4	8	0	1	1	1	6
Surgical patient in-patient	12	0				0			12

* Hemagglutination-inhibition or complement-fixation titers 1:640 or 1:32, respectively.

of unknown origin. Of three patients with chikungunya virus infections, two were hospitalized with a clinical diagnosis of hemorrhagic fever and one patient not hospitalized. Three other patients had a clinical diagnosis of hemorrhagic fever, but virus isolation and serologic studies failed to reveal viral etiology. Ten hospitalized patients with miscellaneous febrile syndromes and 6 out-patients were negative for chikungunya or dengue infection. Finally, 12 surgical in-patients were also virologically negative.

Collection of medical specimens. As soon as possible following admission and always within 24 hours, heparinized blood samples were obtained from each patient (acute specimens). Syringes were rinsed in a 1:20 dilution of heparin sodium * containing 20,000 USP units per ml and heparin expelled before venepuncture. This amount of heparin had no detectable virucidal effect. With rare exceptions at least one subsequent blood sample was obtained 7-21 days after the onset of illness from all studied patients (convalescent specimen). Blood specimens were kept 4° C for several hours until centrifuged and plasma was separated. Portions of the acute specimen were inoculated fresh into suckling mice for virus isolation; other portions were saved at -20°C and -70°C, respectively, for serology and biochemical determinations.

* Organon

Hematology specimens were obtained within 24 hours of admission on all patients; urine and stool samples were collected on selected in-patients.

Clinical laboratory. Complete urinalysis and daily white blood cell count, differential, microhematocrit, Sahli hemoglobin, red blood cell count and platelet count were performed by a single technician. Platelet counts performed for the first 3 weeks of study (until September 7) were by the direct method using Rees-Ecker solution and thereafter by phase microscopy. Tourniquet test was performed by inflating a sphygmometer cuff on the arm to midway between systolic and diastolic pressure for 8 minutes. Appearance of petechiae was graded qualitatively and end points were usually distinctly negative or positive.

Biochemistry. Serum glutamic oxaloacetic transaminase (SGOT), bilirubin, electrolyte determinations, alkaline phosphatase, lactic dehydrogenase, (LDH) and protein electrophoresis were performed on heparinized plasmas at the Biochemistry Department, Walter Reed Army Institute of Research by standard methods.

Virology. Virologic studies consisted of virus isolation attempts and serologic examination of paired plasmas. Virus isolation attempts were made by inoculation of fresh plasma from the acute phase of illness intracerebrally (IC) and intraperitoneally (IP) into 1 day old mice. Plasma was diluted 1:4 in phosphate buffered saline (PBS) and inoculated 0.01 ml IC and 0.02 ml IP into 2 litters of 1 day old mice. Mice were observed for 10 days for signs of illness and then were sacrificed and pooled and brain suspensions passaged. The second mouse passage was treated similarly. Third mouse passage was observed for 21 days, then discarded. Viruses isolated were identified by tissue culture neutralization test by a method described previously (10). Hemagglutination-inhibition (HI) and complement-fixation (CF) tests were performed on plasmas by standard methods (11, 12) using Microtiter* equipment (13). Criteria adopted for evidence of dengue virus infection were either virus isolation with rising dengue HI antibody titer in acute and convalescent specimens, a four-fold or greater rise in HI or CF antibody to dengue virus types 1-4 or high fixed HI titers of 1:640 or CF titer of 1:32 in acute and convalescent serum samples. Chikungunya infections were determined by virus isolation and/or four-fold or greater rise in HI antibody to chikungunya virus in paired sera.

Results.

Hospitalized dengue-virus infections. (52 patients) (dengue hemorrhagic fever).

Age, sex, and ethnic distribution. Patients ranged in age from eight months to 12 years; only 3 patients were below 2 years of age; 22 were male and 30 female. Thirty-one patients were Thai and 21 Chinese.

Course of the disease. The progression of illness in dengue virus infections in the studied children was characteristic. Dengue patients have a first phase

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Table II

COMPARATIVE SYMPTOMS OCCURRING DURING THE PRE-HOSPITALIZATION ILLNESS OF SEVERE, MODERATE AND MILD DENGUE VIRUS INFECTIONS IN ASIAN CHILDREN, CHILDREN'S HOSPITAL, BANGKOK, 1962

Symptoms	PATIENT GROUP		
	Severe (with shock or coma) 4deaths	Moderate (hospitalized illness)	Mild (non-hospitalized)
Total	15	37	8
Days of Illness 1-2	1	8	2
3-4	3	28	1
5 +	11	1	5
Fever	15	37	8
Anorexia	12	13	8
Vomiting	11	27	4
Headache	7	12	4
Abdominal pain	7	12	4
Cough	8	5	2
Melena	2	1	0
Cool extremities	4	8	1
Rash	0	4	0
Arthralgia	3	0	0

Table III

CONCURRENCE OF SELECTED SIGNS AND SYMPTOMS IN CONFIRMED DENGUE AND NON-DENGUE INFECTIONS IN ASIAN CHILDREN, BANGKOK, THAILAND, 1962

Concurrence of signs or symptoms	Hospitalized dengue (hemorrhagic fever)		Non-hospitalized dengue		Miscellaneous infections non-dengue, non-chikungunya	
	1-2 days fever before hosp.	3 or + days fever before hosp.	1-2 days fever before OPD visit	3 + days fever before OPD visit	1-2 days fever before visit or hosp.	3 or + days fever before visit or hosp.
A *, B *, C *, D*	1	9	0	0	0	0
A B C	6	33	0	1	0	1
A C	6	35	0	1	0	1
A	7	35	1	2	0	2
B	7	39	1	4	0	4
C	6	42	0	1	1	3
Fever only	0	2	1	2	4	6
Total patients in group	8	44	2	6	5	11

A * = Positive tourniquet test

B = Other hematologic abnormality i.e. thrombocytopenia, petechiae, purpura, ipistaxis, hematemesis, melena.

C = Hepatomegaly

D = Shock

illness followed by a worsening in the general condition resulting in the child's hospitalization. Postponement of hospitalization may adversely effect the course of disease since children with the most severe hospital course had been sick longer before hospitalization than less severely ill children (Table 2). The crisis of the disease is reached during the 1st or 2nd hospital days and once past is generally followed by rapid improvement. The total duration of illness from the onset or symptoms to the absence of signs of ill health varied from 3-25 days. Only 8 patients had a total period of illness of 5 days or less. This group included three children whose disease was terminated by death. A 6-15 day range included 76 percent of the patients.

Pre-hospitalization illness. Dengue infections began abruptly with onset of fever and progressive malaise. During the next 24-120 hours the most frequent complaints were headache, vomiting, abdominal pain, cough and coryza. Regardless of the ultimate severity of disease, symptoms in this first phase illness were similar in character and frequency (Table 2). These symptoms persisted between 1 and 9 days before hospitalization, 83% of patients were sick for 3 or more days before hospitalization. As seen in Table 3, children with a history of 3 or more days fever who on examination had a positive tourniquet test accompanied by evidence of either bleeding tendency and/or hepatomegaly with rare exception had a dengue virus infection.

Clinical findings in hospitalized patients. General. Fever was invariably present and was usually moderate in the range 101°-103°F with only rare temperatures recorded over 104°F. There was no "typical" fever curve; many patients showed marked temperature fluctuation during their febrile period. Fever was the chief complaint in the majority of patients (76.3 percent) followed by headache (8.9 percent), coldness of the extremities (6.6 percent) and malaise (4.9 percent).

Circulatory. (12 patients) Shock. The most feared and life threatening manifestation of Thai hemorrhagic fever was acute circulatory failure or shock which in previous clinical studies has been said to occur in 7 (14) to 40 percent (15) of cases. It may be that this considerable discrepancy in incidence stems from differences in diagnostic criteria. In this study shock was defined as a syndrome characterized by diastolic and systolic hypotension or narrow pulse pressure (20 Hg or less), tachycardia, a weak, thready pulse, cold moist skin, cool extremities, pallor, with apprehension, restlessness, and frequently disorientation. This syndrome was observed in 12 patients. Shock was present on admission in ten of the twelve and in the two others developed on the second and third hospital days, respectively. Four patients died, one on the 1st, 2 on the 2nd, and 1 on the 3rd hospital day. One patient, a 3 year old girl, 12 hours before her death, had a serum potassium of 5.9 mg/L and an electrocardiogram several hours later showed high peaked T waves, diffuse lowering of the R waves and deepening of the S waves in the precordial leads all suggestive of hyperkalemia.

Electrolyte determinations on plasmas obtained early in hospital course in this group of patients were frequently abnormal. Only one patient out of 10 in whom electrolyte determinations were obtained had normal values for Na^+ , Cl^- or K^+ . No child had overt edema. All had hepatomegaly and serum GOT levels were uniformly elevated, three of the children manifesting levels greater than 200 units. All but one had petechiae and 10 had a positive tourniquet test. All had thrombocytopenia and 11 had leukocytosis. There appeared to be no age group particularly susceptible to acute circulatory collapse although no child with shock was under 3 years of age. Serial hematocrit determinations were inordinately high on admission or fell rapidly following the initiation of intravenous fluid therapy in six of eight patients on whom such data are available. Two of four patients on whom chest X-rays were obtained had small right-sided pleural effusions.

Gastrointestinal. Gastrointestinal tract complaints were extremely prominent and no patient failed to manifest some symptom or sign referable to the enteric canal or accessory organs. Abdominal pain, occasionally localized to the epigastrium but more frequently of a more diffuse character was present in 66 percent of patients. Abdominal tenderness to palpation without muscular rigidity or rebound occurred in 28 of 52 patients. Vomiting was the single most prominent sign of gastrointestinal involvement and was present at some time in 75 percent of patients. There were no distinguishing characteristics and it was neither pernicious nor projectile. Melena was present in 8 children, all of whom had concurrent marked thrombocytopenia. Anorexia was the rule, diarrhea was rare, and constipation, occasionally progressing to almost frank obstipation, was present in over half the patients.

Unequivocal hepatomegaly was observed in 48 of 52 patients. It was not unusual for a patient to show striking changes in liver size over a 48-72 hour period. Several patients who manifested no liver enlargement on admission rapidly developed hepatomegaly over the next few hospital days with gradual regression to normal over the subsequent several days. Liver enlargement was very rarely extreme and despite the rapid size fluctuations, a sharp liver edge could usually be palpated. Tenderness to palpation over the enlarged liver was frequently, but by no means always, elicited. Jaundice was rare, scleral icterus occurring in two patients.

Of patients who manifested hepatomegaly in whom SGOT values were obtained, elevations were observed in 38 of 44 or 86 percent; in seven of these patients (16.3 percent) the SGOT level exceeded 200 units. Serum alkaline phosphatase levels were not elevated. A splenic tip was palpable on deep inspiration in only two patients.

Hematologic. One or more abnormalities referable to capillary fragility, circulating platelets, or hemorrhagic phenomena occurred in 51 or 98 percent of the patients studied. Thrombocytopenia, usually to a severe degree was present at least transiently in 88.3 percent of 43 patients studied and the Rumpel-Leeds test was positive in 78 percent of patients tested. The platelet count was less

Table IV

COMPARATIVE CLINICAL FINDINGS IN SEVERE, MODERATE AND MILD DENGUE INFECTIONS
IN ASIAN CHILDREN, CHILDREN'S HOSPITAL, BANGKOK, 1962

<u>Finding</u>	<u>Severe</u>	<u>Moderate</u>	<u>Mild</u>
	15 patients with shock or coma	37 hospitalized patients	8 out-patients
	No. pos/ /tested	No. pos/ /tested	No. pos/ /tested
Fever	15/15	36/37	8/8
Hepatomegaly	15/15	33/37	1/8
Pos. tourniquet test	13/15	30/37	3/8
Petechiae	12/15	26/37	1/8
Purpura	10/15	12/37	0/8
Restlessness	12/15	18/37	2/8
Cool extremities	13/15	28/37	2/8
Shock	12/15	0/37	0/8
Coma	13/15	0/37	0/8
Abdominal tenderness	7/15	21/37	2/8
Cough	9/15	16/37	2/8
Coryza	5/15	6/37	3/6
Sore throat	2/15	8/35	3/6
Pharyngeal inflammation	5/14	8/36	0/8
Babinski	3/15	2/37	0/8
Pleural effusion	4/7	1/2	0/8
Melena	5/15	3/37	1/8
Hematemesis	1/15	0/37	0/8
Epistaxis	0/15	5/37	2/8

Table V

OCCURRENCE OF SELECTED LABORATORY ABNORMALITIES DURING THE ACUTE FEBRILE PHASE OF DENGUE
IN ASIAN CHILDREN, CHILDREN'S HOSPITAL, BANGKOK 1962

<u>Abnormality</u>	<u>Normal Value</u>	<u>Severe</u> (15 pts)	<u>Moderate</u> (37 pts)	<u>Mild</u> (8 pts)
Thrombocytopenia	< 150,000/mm ³	13/14	26/30	4/6
Leucocytosis	< 10,000/mm ³	14/15	19/32	1/6
Alk. phosphatase	< 6.75 SU/ml	0/14	1/34	1/4
LA peptidase	< 230 u	1/13	0/32	1/4
SGOT 200u	< 50 u	5/14	2/34	1/4
SGOT 50-200u	< 50 u	8/14	24/34	2/4
Total bilirubin	< 1.0 mg/ml	1/5	0/16	-
Hypochloremia	> 100 meq/L	6/14	5/34	0/4
Hyperchloremia <2 yrs <2 yrs	< 115 meq/L < 110 meq/L	3/14	10/34	2/4
Hyperkalemia	< 5.6 meq/L	2/14	1/34	1/4
Hypokalemia	> 3.5 meq/L	4/14	13/34	0/4
Hyponatremia	> 133 meq/L	8/14	5/34	0/4
Lactic dehydrogenase	> 600 u	5/9	4/24	0/2

than 50,000/mm³ in 17 of the 38 patients with thrombocytopenia and less than 25,000/mm³ in 9 patients. Scattered petechiae were present in 38 patients, three other children had a diffuse petechial rash. Palatal petechiae were not infrequently seen. Ecchymoses were common as was bleeding at venipuncture sites. Hemostatic abnormalities in Thai hemorrhagic fever have been studied in some of these patients by Weiss (16).

Nervous System. Because previous studies have omitted mention of CNS findings, particular attention was given to detailed neurological evaluation. Such non specific CNS disturbances as headache, lethargy and restlessness were common, but more definite indications of neurologic involvement were associated only with severe shock. Coma or deep stupor was noted in 13 patients and in 10 of these patients, the comatose state was intimately associated with peripheral circulatory collapse and shock.

Coma and shock. (10 patients). In four patients with coma and shock, the mental obtundation cleared promptly after the restoration of normal blood pressure levels. In one child restoration of normal blood pressure was followed by several days of gradually decreasing mental torpor which eventually cleared completely. Another child who was minimally hypotensive on admission, became comatose coincident with the sudden onset of severe hypotension. Despite a fairly rapid restoration of an adequate blood pressure over a several hour period, marked neurological abnormalities and a semicomatose state with a spastic paresis of all extremities, absent superficial abdominal reflexes and other signs of an upper motor neuron type involvement persisted unabated for 4 weeks until his transfer and loss to follow-up. The last four children in this group sustained the sudden onset of irreversible shock and coma and died early in their hospital course.

In two of the three patients who were comatose without evidence of circulatory collapse, the mental abnormalities were transient, unassociated with other neurological abnormalities and cleared within 48 hours. In the third patient, coma was more prolonged and was associated with other neurological abnormalities of cranial nerve function; there was gradual complete mental clearing over a 10 day period with no evidence of neurological sequelae. Although there was no evidence of circulatory collapse in these latter three patients, it is conceivable that a transient unnoticed hypotensive episode occurred and was responsible for the observed neurological deficits.

There was a history of grand mal type convulsions in two patients. Both of these patients were brought to the hospital shortly after the convulsive episode and each was noted at the time of admission to have fever over 104° F though less than 105° F. It is difficult to appraise the significance of this because temperature recording methods were not standardized as to rectal, oral, or axillary method. One child, while in shock, had repeated Jacksonian type clonic seizures involving the left upper extremity.

Hypoactive deep tendon reflexes were commonly seen, usually in association

with malaise and lethargy. Five children were noted to have pathological reflexes, usually an extensor planter response; three of these patients had associated shock, hypotension, or mental aberrations. In all patients abnormal reflexes disappeared during convalescence.

Respiratory. There has been considerable disagreement concerning the incidence and importance of respiratory symptomatology in Thai hemorrhagic fever. Nelson (7), for example, reported that cough was noted in 40 percent of cases and later stated (17) that "at least 90 percent of the patients have a severe cough, and it hangs on for several days". Toochinda (18), however, reported seeing no children with cough among 1559 patients with suspected Thai hemorrhagic fever admitted to the Siriraj Medical School Hospital between 1951 and 1958. Nelson (7) reported a very high incidence of bronchopneumonia (60 percent) and plural effusion (22 percent) with radiographic confirmation which is in disagreement with rare incidences reported in 1961 by other Bangkok pediatric services (14, 15, 18).

Cough was observed in 24 patients and pleural effusion was noted in 6 of 15 patients examined roentgenologically. In one such patient the effusion was left-sided and was associated with a small area of left lower lobe bronchopneumonia. In the 5 others the effusion was right sided. Because films were taken with patient in a recumbent position, it was difficult to determine whether there was an underlying pneumonic process. In addition to these six patients, a 4 month old child who had a classical clinical picture of THF without a diagnostic serologic response in a 10 day convalescent serum, also had a right-sided pleural effusion noted by X-ray without evidence of underlying pulmonary pathology. It is unfortunate that so few X-ray studies were performed on our patients. Despite this our results support Nelson's observations concerning the frequency of respiratory findings.

Miscellaneous. Two patients had peculiar transient "erythema multiforme like" target-shaped skin lesions scattered on the body. These consisted of a central erythematous punctum surrounded by an erythematous areola which was separated from the central area by a concentric circle of normal skin color. These areas were approximately 1-1.5 cm. in diameter, blanched on pressure, occurred during a period when each child was acutely ill, and spontaneously disappeared within several hours. A diffuse petechial rash was seen in three patients. Maculopapular rashes were observed in 5 other patients. Facial pallor was seen in some children, while a diffuse erythematous facial flush was noted in several other patients during the febrile period. Generalized lymphadenopathy occurred in 48 percent of patients. Small, shotty, non-tender nodes were palpable in the cervical, inguinal and axillary regions. Generalized lymphadenopathy was only slightly more common in patients with THF, however, than in unselected febrile and afebrile control patients and seldom was marked. Arthralgia of a migratory nature involving the knees, hips, shoulder and elbows was noted in three patients. In no case was arthropathy noted and in all patients joint disappeared during early convalescence.

Table VI

STEROID ADMINISTRATION AND LEUCOCYTE RESPONSE
DURING COURSE OF DENGUE HEMORRHAGIC FEVER (42 PATIENTS)

	Progression of differential white blood count during hospitalization			
	Received steroid		No steroid	
	Polymorphonuclear leucocytosis $\geq 50\%$	Lymphocytosis $\geq 50\%$	Polymorphonuclear leucocytosis $\geq 50\%$	Lymphocytosis $\geq 50\%$
Total WBC $>10,000/\text{mm}^3$	18	5	1	4
Total WBC $<10,000/\text{mm}^3$	5	2	1	6

Laboratory studies. A polymorphonuclear leukocytosis was present to a mild or moderate degree in 71 percent of patients studied. An associated "left shift" in the neutrophilic series was present in 61.5 percent of those children with elevated white blood cell counts. Twelve patients showed an early relative or absolute lymphocytosis before developing the neutrophilic response. There were four patients who early in their illness had mild leukopenia ranging from 2200 to 4700/mm³; each of these four on subsequent examination were found to have normal (3) or elevated (1) white blood cell counts. As is shown in table 6, highest leucocyte counts were found in patients treated with steroids.

Most of the children studied were slightly anemic according to U.S. standards but there was no significant difference in convalescent hemoglobin values between children with THF and a group of unselected hospitalized patients without hemorrhagic fever.

Serum lactic dehydrogenase was abnormally high in 6 patients but bore no direct relationship to prominence of neurologic manifestations. Serum alkaline phosphatase elevations were rare. Anuria was never observed and oliguria was extremely rare and transient. A tract to 1+ albuminuria was infrequently seen and was transitory. Random urine specific gravity determinations in general reflected the state of hydration and there was no evidence of a lack of urine concentrating ability. Hematuria was not observed.

Treatment. Therapy was individualized and no attempt was made experimentally to compare various therapeutic regimens.

Intravenous and/or oral corticosteroid therapy was initiated in 38 of 52 hospitalized patients (80.7 percent) and in 1 of 8 patients who were not hospitalized. In addition to parenteral steroids, 11 patients received blood substitutes by transfusion plus parenteral antibiotics, usually chloramphenicol or penicillin and streptomycin. Antibiotics in some form were administered to 53.2 percent of patients and an additional 17.7 percent received sulfonamide therapy. Treatment with Vitamin C parenterally and/or orally was routine for all patients.

Non-hospitalized dengue infections. (8 patients). Two patients were females 7 were Thai, 1 Chinese and all children were older than 6 years. One patient was seen on 3 successive days in the OPD. The 7 others were seen only at the initial visit and fourteen days later when it was determined by a nurse-interviewer that they had not been hospitalized elsewhere. Total duration of illness was not determined due to lack of follow-up. Interestingly, all patients had been febrile for more than 2 days and 5 children had been sick for 5 to 8 days before the OPD visit.

Clinical findings. Chief complaints were fever (8 patients), malaise (2). All patients had a fever of 100°F or higher on examination.

Circulatory. None of the 8 patients were considered to be in shock, although 2 patients had peripheral pulse rates as high as 170. Two patients had cool extremities with warm trunk temperature but none were cyanotic or showed circum-oral pallor.

Gastrointestinal. Seven patients complained of generalized or localized abdominal pain, 7 were anorexic and 4 had at least one episode of vomiting. On examination 2 children had abdominal tenderness and one had moderate hepatomegaly with a SGOT of 200 and an alkaline phosphatase of 10.0 units. One other of 4 patients tested had a mildly elevated SGOT.

Hematologic. Three of eight patients had a positive tourniquet test. Of 4 patients with platelet counts performed all were low, 2 were 80,000/mm³ or below. One patient had palatal petechiae. None had petechiae in other locations. Two had had epistaxis; none had hematemesis, melena, purpura or rash. The patient with palatal petechiae had a positive tourniquet test and a platelet count of 80,000/mm³.

Respiratory. Three children complained of sore throat, 2 had cough, and 3 had coryza. Four of 7 children examined had pharyngeal inflammation. No other findings referent to the respiratory system were observed on physical examination. No X-rays were obtained in this group.

Nervous system. All patients complained of headache. No patient had a

stiff neck or reflex abnormalities. Five patients were described as lethargic, 2 were restless and irritable, but none had any evidence of seriously altered mental or emotional status.

Miscellaneous. Of 6 patients studied only 1 had a leucocytosis of greater than 10,000/mm³. Of 4 patients studied, none had abnormalities of serum electrolytes. No patients complained of arthralgia. Four of 8 had generalized lymphadenopathy.

Chikungunya disease. Chikungunya virus, a group A arbovirus responsible for dengue-like diseases in Africa, is disseminated in Bangkok during epidemics of Thai hemorrhagic fever (5). During the 1962 outbreak illnesses due to this virus were responsible for 10-15% of Children's Hospital admissions with a diagnosis of Thai hemorrhagic fever (19). For this reason study of the clinical manifestations of chikungunya infections in Asian children is of importance. Unfortunately, only 3 proven chikungunya infections are included in this series. A typical illness is presented in the appendix (case 5).

In this very small number of cases, chikungunya infections differed from most dengue illnesses in the following respects.

1. The short interval between onset of fever and occurrences of maximal symptoms.
2. Absence of shock, hematemesis or melena.
3. Absence of marked hepatomegaly.
4. Total white blood count was normal or leucopenic with relative lymphocytosis.

Further observations will be required to extend information regarding the nature of chikungunya viral syndrome.

Discussion: It was the purpose of this investigation to study the full spectrum of dengue virus illness as presented to the practising physician in Thailand. A conscious attempt was made to avoid selection of patients by a pre-determined criteria or by influencing admission policy either specifically or generally. Hospitalized febrile syndromes other than hemorrhagic fever were included in the study. Hospital admission was influenced by the patient's condition as well as parental anxiety and bed space. When beds were available, milder illnesses were admitted than when bed space was limited. Parental anxiety was an important factor influencing admission since Children's Hospital has 30 private beds to which such patients could be admitted.

Despite the absence of firmly established criteria or pathognomonic signs for diagnosis or hospitalization of Thai hemorrhagic fever, the observed hospitalized

dengue disease fell into several clearly defined and closely associated symptom complexes. The most common concurrence of symptoms was a fever for 3 or more days before hospitalization plus hepatomegaly. Two thirds of all admitted patients had these two findings plus a positive tourniquet test and other evidence of hemostatic abnormality. On the other hand, only 1 of 8 virologically confirmed non-hospitalized dengue infections and 1 of 16 miscellaneous hospitalized febrile disease not dengue or chikungunya presented with this quartet of findings. Since virological confirmation of clinical hemorrhagic fever diagnosis exceeded 90% in over 400 patients studied at Children's Hospital in 1962 (19) and large numbers of patients admitted with other diagnoses and confirmed as dengue were not found, it may be concluded that Thai hemorrhagic fever is a unique and definable clinical syndrome and that clinical diagnosis under epidemic conditions is accurate.

This investigation suggests that the dengue hemorrhagic fever syndrome is biphasic. The first phase consists of a non-descript febrile illness characterized by fever, headache, upper respiratory symptoms, abdominal pain and occasionally nausea or vomiting. The second phase is characterized by hemorrhagic phenomena, hepatomegaly, shock and manifestations of altered capillary permeability such as pleural effusion. For the majority of children the first phase illness probably constitutes the total disease response.

Some children, however, progress to the second phase of hemorrhagic fever. The quandary of the conscientious physician in attempting to assign the correct diagnosis, prognosis and management to a patient with a non-descript illness during a hemorrhagic fever outbreak can readily be imagined. The protean manifestations of milder and less complicated dengue virus infections studied suggest that it might be difficult, if not impossible, to separate this disease from a variety of respiratory or enterovirus infections which also produce all ill defined febrile illnesses. A majority of patients with dengue virus infection seen in the out-patient department in this study received a diagnosis of upper respiratory infection. The observed frequency of cough, coryza and pharyngeal inflammation makes this a reasonable diagnosis.

The second phase dengue infection (hemorrhagic fever) emerges as a complex pathogenetic process involving every major organ system except the genitourinary tract. Involvement of the cardiovascular system is demonstrated by increased capillary fragility, by increased capillary permeability (pleural effusions, decreased circulation blood volume manifested by increased hematocrit) and by shock. Cardiovascular instability with fluid shifts accompanying dengue virus infection probably presents the greatest threat to the life of children. The G.I system is also affected, the most prominent manifestations being hepatomegaly and bleeding. Pathologic studies in Thailand have shown scattered foci of hyaline or acidophilic necrosis, edema and congestion in autopsy livers from hemorrhagic fever patients (20). Abdominal pain, generalized or localized, observed in 2/3 of patients, only rarely appeared to originate in the liver. The pathogenesis of this symptom is unknown. In the respiratory system cough,

coryza and pharyngeal inflammation were common findings in both severe and mild cases. Pleural effusions and/or bronchopneumonia were found with high frequency in 15 patients examined by X-ray. Hematopoietic abnormalities regularly occur in second phase dengue illness. Abnormalities in the bone marrow in hemorrhagic fever have been discussed by several authors (16, 21). There appears to be a suppression of 1 or more cellular elements of the marrow during infection. The degree of central nervous system involvement remains unsettled. While a number of children, particularly those with severe disease were comatose and exhibited transient reflex changes and many children manifested irritability, lethargy and changes in personality, it is not certain that these findings exceed those accompanying other severe febrile infections. Central nervous system manifestations of dengue infection should be evaluated further in future studies.

Lymphadenopathy, leucopenia, arthralgia and a saddle back temperature curve, the hall marks of dengue virus infection in Caucasians, were conspicuously absent in hemorrhagic fever patients. Shotty pea-sized lymph glands were felt in the cervical, inguinal and axillary regions of the majority of children. However, lymph nodes of the same size and consistency were palpable in 12 surgical patients and 16 patients with miscellaneous febrile diseases. In most instances, lymph node enlargement could be explained by skin abrasions, superficial skin infections or periodontal infections and it is questionable whether lymphadenopathy was due to dengue infection. Normal or low total white cell counts were noted early in the course of illness in many children hospitalized with dengue virus infection. Over 2/3 of patients studied developed WBC of 10,000/mm³ or greater during the course of hospitalization. Patients with marked WBC elevations were in general more severely ill. These patients also were given cortisone, a polymorphonuclear leucopoietic stimulant, plus multiple other medications. In some instances cutdown site infection or occult infection may have been responsible for leucocytosis. However, along with high total white blood cell counts, many children developed a relative lymphocytosis with frequent Turck reaction cells. This reaction would not be expected with cortisone administration. Leucocytosis maybe a part of the disease response to dengue infection in Asian children but this observation requires further careful evaluation.

This final observation illustrates an important deficiency in the present study. Because of therapeutic intervention the natural history of Thai hemorrhagic fever has not been elicited. Many elements in the therapeutic management of the studied patients may have influenced the severity and duration of illness as well as of biochemical abnormalities (e.g. effect of steroids on serum electrolytes). Particular attention should be given in future studies to the need for broad spectrum antibiotics and steroids commonly employed in Thailand and to attempt to separate clinical or laboratory findings resulting from therapy from pathophysiologic disturbances due to the disease process alone.

No comment can be made from this study to explain why the described dengue illnesses varied so markedly from the dengue fever syndrome seen in other racial groups in Thailand or in other dengue fever outbreaks in different areas in the

world. Future studies of the biologic properties of the causative agent and the pathologic physiology of dengue infections hopefully will shed more light upon this paradox.

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APPENDIX

Case 1. (PUO 47) Mild dengue illness.

K.S., an 8 year old Thai male, first seen in Children's Hospital out-patient department on August 22 with history of fever for the preceding 6 days. On 16 August child complained of sore throat and fever, was taken to a doctor and received an injection of an unknown medicine. On the next day the patient was vaccinated at school. He continued to be febrile with increasing malaise, lethargy and anorexia until the OPD visit. On examination he had a fever of 103.5°F, blood pressure 110/70, pulse rate of 120 with a respiratory rate of 16. The patient complained of headache and intraepigastric pain. On abdominal examination no organs were palpated and no tenderness elicited. A tourniquet test was negative. Ear lobe bleeding time was 2 minutes. Venous clotting time was 6 1/2 minutes.

The patient was placed on chloramphenicol, vitamin C and oral prednisone. He was seen in study on the next successive two days. On the 3rd OPD visit the patient was nearly afebrile. Blood pressure remained normal, pulse rate fell to 84. On 23 August the child had one bout of loose stools and the same evening had a small epistaxis. The patient did not have pharyngeal injection, petechiae, rash or positive tourniquet test during the period of observation. Significant laboratory findings are as follows:

Case 1.

Date	Aug. 22	Aug. 23	Aug. 24
Day of illness	7	8	9
WBC: /mm ³	7,900	8,000	5,300
% Polys	78	48	39
% Stabs	5	2	2
% Lymphs	22	50	59
% Eos		1	2
% Monos		1	1
Hgb: gm%	11.5	12.0	12.0
Hct: %	40	42	38
Platelets: mm/ ³	180,000	380,000	240,000
SGOT: units	32	28	
Total bilirubin: mg%	0.5		
Na: meq/L	140	140	
Cl: meq/L		118	
K: meq/L	4.5	3.8	

VIROLOGY.

	HI Titer		Virus isolation	Inter-pretation
	Chikungunya	Dengue		
22 August 1962	40	10,240	neg.	Dengue
8 September 1962	40	5,120		

Case 2. (HFI 77) Moderate dengue illness.

M. S., a 9 year old Chinese girl, was admitted to the Children's Hospital on 24 August with a 7 day history of fever, malaise, constipation and very localized infraepigastric abdominal pain of varying severity. She had had a slight sore throat and generalized headache coincident with the onset of the illness but these symptoms had disappeared by the time of admission. Physical examination revealed the child to be very restless and irritable; the temperature was 100°F, the pulse full and regular and respirations unlabored at 20/minute. There were small non-tender lymph nodes palpable in the cervical and inguinal regions, many petechiae were noted on the hard palate and there was tenderness to palpation in the epigastrium. The lower extremities were cool and the remainder of the body quite warm. The remainder of the physical examination was normal. The 8 minute tourniquet test was positive. Therapy on admission consisted of bed rest and oral vitamin C. On the evening of the first hospital day, the child was restless and began to perspire profusely. The blood pressure fell to 96/60 but the pulse rate remained at 86-94/minute. Therapy was instituted with intravenous dextrose in 0.45 percent saline solution containing 50 mg of hydrocortisone and vitamin C; oral prednisolone treatment was begun concomitantly. A very low grade fever was interrupted by spikes to 105°F on 26 and 27 August following which there was gradual decrease.

During the next four hospital days, (25-28 August) the child appeared quite ill with marked malaise, a gradually decreasing fever and extreme irritability and restlessness which at times approached frank delirium. The blood pressure ranged from 96-106 systolic over 60-70 diastolic, the pulse was more rapid, usually in the range 130-135/minute and respirations remained regular and unlabored. Many petechiae were noted over the upper and lower extremities and there were purpuric areas at venepuncture sites. Epigastric tenderness persisted and on 26 August an enlarged tender liver was palpable for the first time. Therapy was continued with intravenous fluids with hydrocortisone, mild sedation and oral prednisolone. In addition she received 350 cc of fresh plasma on 25 August. Antibiotic therapy with penicillin and terramycin was begun on 27 August and discontinued by 2 September. By 29 August the temperature had fallen to normal and the child considerably brighter. Her extreme restlessness and irritability decreased and deep tendon reflexes which had been hypoactive became normal. Increasing pallor was noted, however, and a confirmatory fall in hemoglobin and hematocrit were observed. Hepatomegaly was persistent but abdominal tenderness gradually waned. Obstipation subsided by the first of September. The remainder of her hospital course was uneventful. By 29 August she was afebrile and by 30 August asymptomatic. She was discharged from the hospital on 2 September. Significant laboratory data are shown below:

Case 2

Date	Aug. 25	Aug. 26	Aug. 27	Aug. 28
Day of illness	9	10	11	12
WBC: /mm ³	4,700		15,700	13,400
% Polys	22		64	72
% Stabs	3		19	9
% Lymphs	72		15	19
Hgb: gm%	13		11	9.5
Hct: %	43		38	32
Platelets: /mm ³	130,000		83,000	115,000
SGOT: units	76			84
Total bilirubin: mg%	0.32			1.0
Na: meq/L	131			136
Cl: meq/L	105			108
K: meq/L	3.6			2.8

VIROLOGY

	HI Titer		Virus Isolation	Inter-pretation
	Chikungunya	Dengue		
24 August 1962	20	20	Dengue	Dengue and
9 September 1962	320	160		chikungunya

Case 3 (HF 187) Severe dengue illness.

K. S., a 6 year old Thai girl, was admitted to Children's Hospital on 3 September 1962 because of fever, malaise, abdominal pain and vomiting of four days duration. She had been anorexic and nauseated for this period and had not a bowel movement since the onset of her illness. On the day prior to admission she complained of a mild generalized steady headache. Physical examination shortly after admission showed her to be desperately ill and semicomatose. The temperature was 104°F, blood pressure 70/50, the pulse weak and thready at 150/minute and respirations were regular at 30/minute. She responded to painful stimuli, was restless, perspiring profusely and the skin was cold and clammy. The lower extremities in particular were cold. Deep tendon reflexes were hypoaactive and a right Babinski reflex was elicited. The superficial abdominal reflexes were absent. There were scattered petechiae over the upper and lower extremities and face. A tourniquet test was equivocal. There was diffuse pharyngeal injection, the liver was palpable, and there was pea-sized lymph nodes in the epitrochlear, cervical, axillary and inguinal regions.

Intravenous hydrocortisone, dextrose in 0.45 percent saline, 25 percent salt poor human albumin, and intramuscular hydrocortisone were administered. During the next few hospital days the blood pressure stabilized at 80-90/60 and the pulse rate fell to 120-130/minute with better volume. She remained semicomatose and febrile. On the fourth hospital day she developed left lower lobe pneumonia confirmed by X-ray. She became increasingly pale; the hematocrit fell from 53 percent on the admission to 34 percent over the first four days. She was given a 250 cc whole blood transfusion and intramuscular penicillin and streptomycin were begun 5 September. Streptomycin was discontinued after four days and penicillin after seven days. By the sixth hospital day there was considerable improvement. The child became alert. IV steroids were discontinued and oral prednisolone was substituted. The blood pressure was stable and the pulse fell to below 100/minute. The deep tendon reflexes became normal but the superficial abdominal reflexes were absent throughout her hospitalization. There was gradual improvement. By the 12th day she was afebrile by the 14th day, asymptomatic. She was discharged after 15 days hospitalization. Significant laboratory data is presented below:

Case 3

SEPTEMBER

	3	4	5	6	7	8	9	10	10--15
Date									
Day of illness	4	5	6	7	8	9	10	11--16	
WBC: /mm ³	8,600	18,900	23,600	16,000	9,300				8,900
% Polys	57	38	43	59	63				63
% Stabs	10	3	32	17	13				6
% Lymphs	33	55	25	22	20				29
Hgb: gm%	13.5	13.0	10.5	10.5	10.5				10.0
Hct: %	53	43	35	35	-				34
Platelets: /mm ³	130,000	63,000	60,000	71,000	63,000	53,000			192,000
SGOT: Units	84			194					26
Total bilirubin: mg%				0.1					2.6
Na: meq/L	129			131					139
Cl: meq/L	100			106					113
K: meq/L	4.3			2.7					4.0

VIROLOGY

	Chikungunya	HI Titer	Dengue	Virus isolation	Inter-pretation
3 September 1962	0		40		
15 September 1962	0		10,240		
22 September 1962	0		640	Neg.	Dengue

Case 4. (HF 188) Fatal dengue illness.

Y. C., a 3 year old Thai girl, was admitted to Children's Hospital on 4 September 1962 with the tentative diagnosis of acute Thai hemorrhagic fever. Her illness began with fever, vomiting, coryza, cough and headache 11 days prior to admission. Within the preceding 2 days she had become increasingly lethargic and anorexic. On admission she was very ill with fever to 104°F; the pulse was rapid, weak and thready at 200/minute, the blood pressure 80/40 and there was marked tachypnea of 100/minute. The skin had a faintly cyanotic hue and was cold and clammy. The lower extremities were very cold. Lower extremity pulses were weak but palpable.

The child was only slightly responsive to nociceptive stimuli. The deep tendon reflexes were barely elicitable. Pallor was striking. There were scattered petechiae over the entire body and two small purpuric lesions were present on the face. The tourniquet test, however, was equivocal. The pharynx was diffusely hyperemic. The liver was enlarged 2 finger breadths below the costal margin and shotty lymph nodes were palpable in the cervical, axillary and inguinal regions.

During the first 24 hours of her hospitalization therapy included intramuscular and intravenous hydrocortisone, IV fluids, and human serum albumin. The blood pressure rose slightly. On the morning of the second hospital day, rhonchi were audible over the left lower lobe posteriorly. Shortly thereafter on the same morning her blood pressure fell and she passed a small tarry stool. She received 350 cc of fresh whole blood. A large hematoma was noted at the site of a right femoral venipuncture done the previous day. An electrocardiogram showed high peaked T waves in V₄, V₅, V₆ and deep S waves through V₆ suggestive of hyperkalemia. In the early evening of the second hospital day therapeutic measures the blood pressure suddenly fell to unobtainable levels, and the child died at 1925 hours, never having regained consciousness. Significant laboratory data are shown below:

Case 4

SEPTEMBER

Date	5
Day of illness	13
WBC: /mm ³	19,000
% Polys	57
% Stabs	21
% Lymphs	22
Hgb: gm%	11
Hct: %	35
SGOT: units	250
Serum LDH: units	2,000
Total bilirubin: mg%	1.25
Na: meq/L	126
Cl: meq/L	91
K: meq/L	5.9

VIROLOGY

	HI Titer		CF Titer		Virus isolation	Interpretation
	Chik.	Dengue	Chik.	Dengue		
5 September	0	160	0	16	Neg.	Dengue
6 September	20	160	0	64		

Case 5. (HFI 84) Chikungunya disease.

P. C., a 9 year old Thai male, was admitted to Children's Hospital on August 30 with a chief complaint of fever and arthralgia of the right knee and shoulder of 1 day's duration. On admission the patient had a temperature of 105.8°F. His blood pressure was 110/70, pulse rate was 120/minute and respiratory rate 14/minute. The child was acutely ill, anorexic and complaining of headache. He had a shotty cervical, axillary and inguinal lymphadenopathy. There were scattered petechiae on the extremities. On abdominal examination the liver edge was felt at the costal margin. He complained of pain in the right knee on weight bearing but not on passive motion. The joint was not red or warm to touch. A 8 minute tourniquet test was equivocally positive. Bleeding time was 1 minute 15 seconds and VCT was 4 minutes and 50 seconds.

The patient was treated with intravenous 5% dextrose in water and saline, sedated with luminal and given tetracycline 250 mg QID. On this regimen his fever persisted for a total of 8 days. On 1 September the arthralgia had disappeared. On 4 September a diffuse erythematous macular rash was noted on face, torso and upper extremities. Two days later the rash, fever and all other symptoms disappeared and the patient was discharged.

Case 5

Date	Aug. 31	Sept. 1	Sept. 2	Sept. 3
Day of illness	2	3	4	5
WBC: /mm ³	6,250			5,000
% Polys	65			27
% Stabs	10			6
% Lymphs	24			67
% Eos				
% Monos	1			
Hgb: gm%	11.0			11.0
Hct: %	37			36
Platelets: /mm ³	178,000			236,000
SGOT: units	28			50
Total bilirubin: mg%	0.57			0.67
Na: meq/L	138			140
Cl: meq/L	109			105
K: meq/L	3.9			3.6

VIROLOGY

	HI Titer		Virus isolation	Inter-pretation
	Chikungunya	Dengue		
31 August 1962	0	320	Chik.	Chik.
7 September 1962	20	640		
13 September 1962	1,280	640		