

2. Hematologic evaluation of 27 dengue confirmed hemorrhagic fever cases performed by Captain H. Weiss, September 1962 and,

3. Clinical and clinical laboratory investigation of over 500 hemorrhagic fever patients by Dr. Suchitra Nimmannitya, Children's Hospital in 1962-1964.

Progress: Clinical studies of hospitalized Thai and Chinese children with dengue and chikungunya disease in 1962 are summarized below:

Hospitalized dengue virus infections. Fifty two patients with dengue hemorrhagic fever were studied.

Control of the disease. The progression of illness in dengue virus infections in the studied children was characteristic. Dengue patients have a first phase illness followed by a worsening in the general condition resulting in the child's hospitalization. The crisis of the disease is reached during the first or second hospital days and once past is generally followed by rapid improvement. The total duration of illness from the onset to the disappearance of symptoms 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 per cent 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 1). 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 2, children with a history of 3 or more days fever, who on examination had a positive tourniquet test accompanied by evidence of 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 temperature 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 per cent) followed by headache (8.9 per cent), coldness of the extremities (6.6 per cent) and malaise (4.9 per cent).

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 to 40 per cent of cases. Shock was defined as a syndrome characterized by diastolic and systolic hypotension or narrow pulse pressure (20 mm Hg or less), tachycardia, a weak, thready

Table 1

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	Severe (With shock or coma) 4 deaths	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 2

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, epistaxis, hematemesis melena.

C = Hepatomegaly

D = Shock

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 first, two on the second and one on the third hospital day. Twelve hours prior to death, a three year old girl 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. All patients 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, but fell rapidly following the initiation of intravenous fluid therapy in six of eight patients on who 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 common. Abdominal pain, occasionally localized to the epigastrium but more frequently of a more diffuse character was present in 66 per cent of patients. Abdominal tenderness to palpation without muscular rigidity or rebound occurred in 28 of 52 patients. Vomiting was present at some time in 75 per cent of patients. There were no distinguishing characteristics; 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 live 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 per cent; in seven of these patients (16.3 per cent) 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 per cent of the patients studied. Thrombocytopenia, usually to a severe degree was present at

least transiently in 88.3 per cent of 43 patients studied and the Rumpel-Leeds test was positive in 78 per cent of patients tested. The platelet count was less than 50,000/mm³ in 9 patients. Scattered petechiae were present in 38 patients; three other children had a diffuse petechial rash. Ecchymoses were common as was bleeding at venipuncture sites. Hemostatic abnormalities in Thai hemorrhagic fever have been summarized in the Annual Report for FY 1964.

Nervous system. Such nonspecific CNS disturbances as headache, lethargy, and restlessness were common, but more definite indications of neurologic involvement were associated 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.

In four of 10 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. 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 plantar response; three of these patients had associ-

ated shock, hypotension, or mental aberrations. In all patients abnormal reflexes disappeared during convalescence.

Respiratory. 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 recumbant position, it was difficult to determine whether there was an underlying pneumonic process.

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 *æ*ola 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 per cent 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 pain disappeared during early convalescence.

Laboratory studies. A polymorphonuclear leukocytosis was present to a mild or moderate degree in 71 per cent of patients studied. An associated "left shift" in the neutrophilic series was present in 61.5 per cent 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. The 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 differences 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 trace to 1⁺ albuminuria was infrequently seen and was tran-

sitory. 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.

Non-hospitalized dengue infections. (8 patients).

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. A second 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 $80,000/\text{mm}^3$ 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 $80,000/\text{mm}^3$.

Respiratory. Three children complained of sore throat, 2 had cough, and 3 coryza. Four of 7 children examined had pharyngeal inflammation. No other findings referable 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. Two were restless and irritable, but none had any evidence of seriously altered mental or emotional status.

Miscellaneous. Of six patients studied, only one had a leucocytosis of greater than $10,000/\text{mm}^3$. No patients complained of arthralgia. Four of eight had generalized lymphadenopathy.

Chikungunya Disease.

Chikungunya virus, a group A arbovirus responsible for dengue-like disease in Africa, is disseminated in Bangkok during epidemics of Thai hemorrhagic fever. 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. The day of hospitalization in 20 chikungunya virus infections is summarized in Figure 1. As shown, chikungunya is an illness with abrupt onset in which maximum prostration occurs within the first 2 days after the onset of fever. A positive

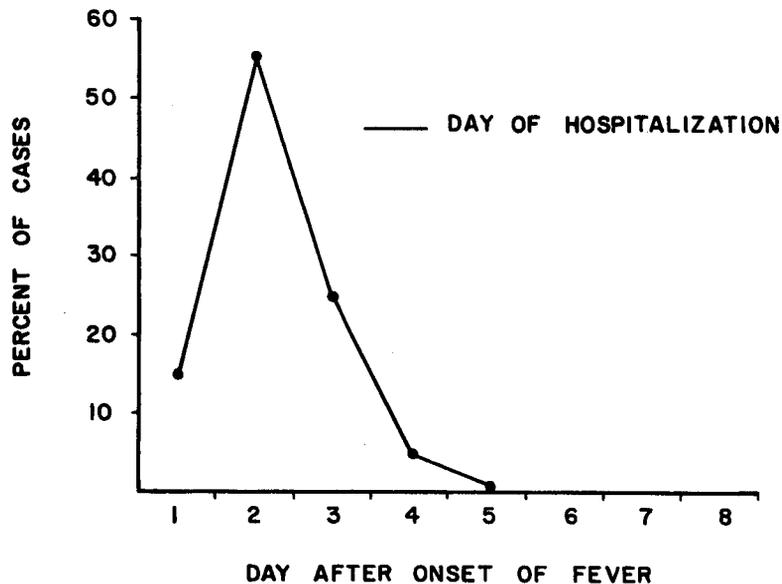


Figure 1.

DAY OF HOSPITAL ADMISSION AFTER ONSET OF FEVER IN 20 CHIKUNGUNYA INFECTION IN THAI AND CHINESE CHILDREN, CHILDREN'S HOSPITAL, BANGKOK, 1962-3. ADMISSION OCCURRING WITHIN 24 HOURS OF ONSET OF FEVER RECORDED AS DAY 1.

Table 3

COMPARISON OF SELECTED CLINICAL FEATURES IN THAI AND CHINESE CHILDREN HOSPITALIZED WITH CHIKUNGUNYA AND DENGUE INFECTIONS (HEMORRHAGIC FEVER), BANGKOK, THAILAND, 1962-3

Finding	PER CENT OCCURRENCE OF FINDING BY ETIOLOGY	
	Chikungunya (20 cases)	Dengue (98 cases)
Pos. tourniquet test	75%	81%
Petechiae	45	62
Epistaxis	10	17
Vomiting	60	63
Abdominal pain	45	50
Lymphadenopathy	50	Similar 38
Purpura	0%	Different 20%
Melena	0	12
Hematemesis	0	12
Hepatomegaly	15	48
Shock	0	35
Cool extremities	15	56
Cyanosis	5	27
Maculopapular rash	50	13
Myalgia	55	10

DURATION OF FEVER IN HOSPITALIZED CHIKUNGUNYA (20 CASES)
AND DENGUE (98 CASES) INFECTIONS

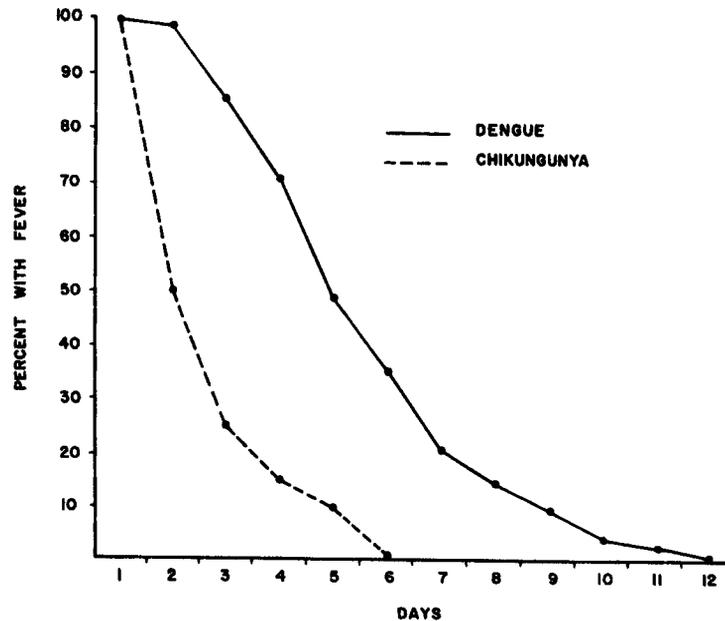


Figure 2.

DURATION OF FEVER IN 20 HOSPITALIZED CHIKUNGUNYA AND 98 HOSPITALIZED DENGUE INFECTIONS IN THAI AND CHINESE CHILDREN, CHILDREN'S HOSPITAL, BANGKOK, 1962-3.

tourniquet test, rash, petechiae and thrombocytopenia are common in chikungunya; however, hepatomegaly, severe bleeding and shock are rare (Table 3). Finally, chikungunya is a shorter illness than dengue hemorrhagic fever (Figure 2). The usual chikungunya infection is readily distinguished from severe hemorrhagic fever, but the distinction between milder dengue infections and chikungunya may be impossible. From these studies chikungunya is no longer considered to be the cause of the severe hemorrhagic fever syndrome but rather an acute febrile disease with occasional hemorrhagic manifestations and a good prognosis.

Summary and Conclusions: Thai hemorrhagic fever is a multiple system disease producing clinical or laboratory abnormalities in the cardiovascular system, bone marrow, liver, lungs and central nervous system. The findings which characterize this infection and serve to distinguish it from other febrile syndromes are the association of acute non-icteric hepatitis, pleural effusion and cardiovascular collapse in a febrile patient. Hemostatic abnormalities occur multiply and are related to loss of megakaryocyte function, possible sequestration of platelets, liver damage affecting the prothrombin and fibrinogen activity and other unelucidated factors responsible for abnormal clotting in siliconized tubes.

Publications:

Weiss, H. J., Halstead, S. B. Studies of hemostasis in Thai hemorrhagic fever. J. Pediatrics. (In press).

Margiotta, M., Nimmannitya, S., Halstead, S. B. Clinical observations on dengue hemorrhagic fever in Thailand. J. Ped. (submitted for publication).