SCOTT B. HALSTEAD*

Virology Department, U.S. Army-SEATO Medical Research Laboratory, Bangkok, Thailand

DENGUE AND HEMORRHAGIC FEVERS OF SOUTHEAST ASIA

During the summer of 1897 the inhabitants of the coastal towns of North Queensland, Australia suffered their fourth consecutive annual visitation of dengue fever. The unusual virulence of this 1897 epidemic engaged the concern of Dr. F. E. Hare of Charters Towers, Queensland, who undertook to write a general description of the outbreak by polling physicians practicing in the region.[1] From 19 correspondents Hare obtained records of 60 fatalities, 30 of these in children. The severe illness in children was most characteristic. Hare remarked that these cases were,

> amongst the most startling that occur in medical practise. In nearly all of these (children) death must be, I think, attributed to the intensity of uncomplicated disease . . . All . . . were previously healthy children; their ages varied between 3 and 14 years . . . The manner of death was in the majority almost identical, very rapid heart failure and collapse (which) occurred at the crisis on the fifth day of fever, and death ensued from two to 48 hours later . . . The patient exhibits all the signs of acute hemorrhage, a frightful restlessness, jactitation, extreme irritability of temper . . . terminating (sometimes) in a state exactly resembling the (shock) stage of cholera.

This account may be the classic description of a disease known today as dengue hemorrhagic fever. In the intervening 68 years, syndromes characterized by severe hemorrhage or shock and death occurring with dengue fever epidemics have been described in the medical literature at least five times: the southern United States in 1922,[2] Durban, South Africa in 1927,[3] Greece in 1928,[4] Formosa in 1931[5] and in various countries of South and Southeast Asia since approximately 1950.[6-10]

The modern recognition of hemorrhagic fever of dengue etiology was made by Hammon and associates who observed an outbreak in Manila, the Philippines in 1956.[6] From patients hospitalized during this outbreak dengue viruses types 2, 3, and 4 were isolated. In rapid sequence this "new" disease was recognized and etiologically associated with dengue viruses in Bangkok in 1958,[6] Singapore in 1960,[7] Penang, Malaysia in

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* Chief, Virology Department.

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1962[11] and South Vietnam[8] and eastern India in 1963.[10, 12] By crediting clinical descriptions, unconfirmed virologically, a pattern of disease occurrence in Southeast Asia for the past 15 years has been constructed as shown in Figure 1. Hospital records of hemorrhagic fever patients have been found in Thailand in every year from 1950.[14] Disease was first

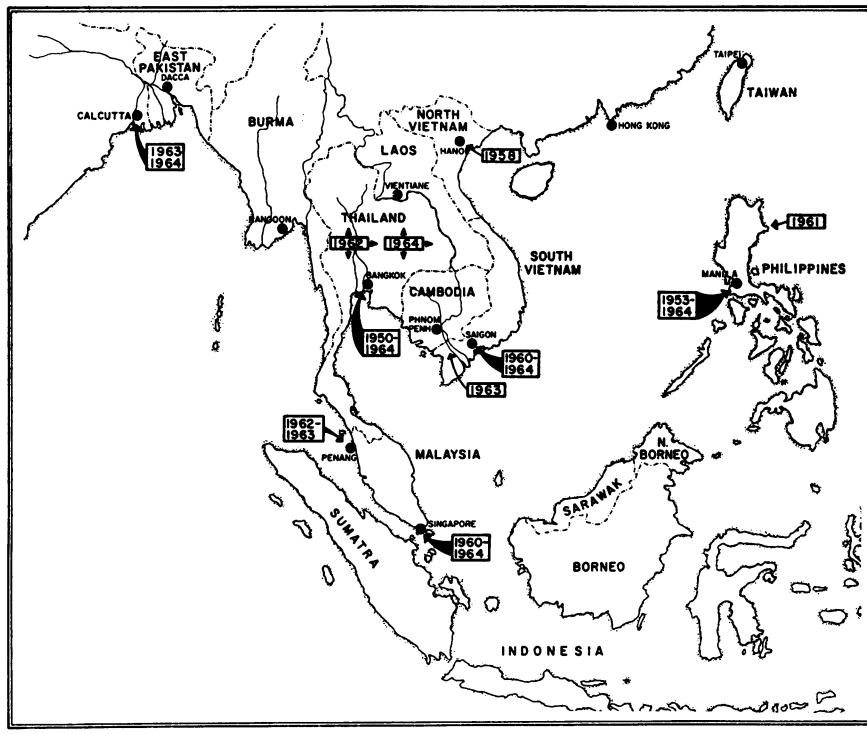

FIG. 1. Distribution of mosquito-borne hemorrhagic fever outbreaks in South and Southeast Asia, 1950-1964. Includes outbreaks established from clinical records of hospitalized patients. After Halstead.[13]

described in the Philippines in 1953, North Vietnam in 1958,[9] South Vietnam in 1960, Singapore and Penang in 1960 and 1962, respectively, and India in 1963. It should be added that a trained observer working continuously in Cambodia since 1961 has reported isolations of dengue viruses but no disease clinically resembling hemorrhagic fever.[15] To date hemorrhagic fever has not been reported from Burma, East Pakistan, or Indonesia.

From October 1961 until the present the Virus Department of the U.S. Army-SEATO Medical Research Laboratory has conducted linear studies

of hemorrhagic fever in Thailand. This period has presented a unique opportunity for the study of human arthropod-borne virus infection. Since the beginning of the study there has not been a single month in which cases of hemorrhagic fever were not admitted to Bangkok hospitals. Over 16,000 Thai and Chinese children were hospitalized with this diagnosis and 1,000 died. A number of clinical and epidemiologic studies have been undertaken.[17, 18, 19] This paper presents in preliminary fashion a brief summary of data illustrating various clinical, etiologic, epidemiologic and control aspects of hemorrhagic fever and finally, a discussion of the diverse questions and hypotheses that are raised in attempting to explain the pathogenesis of this disease.

Much of what is known about hemorrhagic fever is contradictory or complex, not the least of which is its terminology. The term "hemorrhagic fever" was introduced into the American medical literature during the early 1950's in reports of epidemic hemorrhagic fever that occurred among United Nations personnel in Korea.[20] As currently employed, "hemorrhagic fever" is applied to a large number of different arthropod-borne viral illnesses. These diseases are differentiated by naming them for the geographic area in which they occur; e.g., Omsk hemorrhagic fever, Argentine hemorrhagic fever, or Thai hemorrhagic fever. Each is a distinct illness with different clinical manifestations, epidemiologic features, causative agents and vectors. The name mosquito-borne hemorrhagic fever has been proposed for the disease observed in South and Southeast Asia. When etiologic studies allow, the more specific term, dengue, or as the case may be, chikungunya hemorrhagic fever is preferred.

CLINICAL FINDINGS, PATHOLOGY AND PATHOPHYSIOLOGY OF DENGUE HEMORRHAGIC FEVER

Hospitalized cases clinically diagnosed as hemorrhagic fever form two groups based upon clinical findings and prognosis. The first group is comprised of self-limited disease ranging from an undifferentiated fever with a positive tourniquet test or thrombocytopenia to a febrile illness with hemorrhage and hepatomegaly. The milder of these syndromes resemble illnesses seen with many other viral infections. The second group, comprising 30 to 40 per cent of hospital admissions, is uniquely associated with dengue virus infections. These cases, now called hemorrhagic fever with shock or dengue shock syndrome, have a mortality rate as great as 50 per cent. An epitomized description of this severe syndrome follows:

The disease occurs most frequently in children under the age of 13. It begins abruptly with a febrile or minor illness stage characterized by fever,

upper respiratory symptoms, headache, vomiting, and abdominal pain. These symptoms continue for two to four days during which time the child is anorexic but ambulatory and not critically ill.

This stage is followed by an abrupt deterioration in the condition of the patient with the rapid onset of lassitude, weakness, and physical collapse. Most patients are brought to the hospital at this time. On examination the child generally manifests cold, clammy extremities with a warm trunk, flushing of the face, peripheral vascular congestion, restlessness, diaphoresis, and petechiae located most frequently on the forehead and distal extremities and less frequently, a macular or maculopapular rash. There may be circumoral and extremity cyanosis. The pharynx is injected. Systolic and diastolic blood pressures are low or absent or the differential blood pressure (pulse pressure) may be less than 20 mm Hg. There is marked tachycardia with weak, thready pulse and faint heart sounds. The liver is enlarged two or three finger breadths, firm and nontender. There are various changes in state of consciousness, changes in neurologic reflexes, and the appearance of abnormal reflexes may be observed. Occasionally minimal pleiocytosis may be observed in the spinal fluid.

On the fourth or fifth day of illness, and usually within 24 to 36 hours after admission, the severely ill patient is in danger of dying (Fig. 2). Melena, hematemesis, coma, and deepening or unresponsive shock have a grave prognosis. If the period of crisis is survived, children show steady and fairly rapid improvement.

Common admission laboratory findings are a positive tourniquet test, prolonged bleeding time, thrombocytopenia, mild leucocytosis with atypical monocytes, and increased hematocrit and hemoglobin concentration. Bone marrow examination shows maturation arrest of megakaryocytes, an early pancytopenia and a late stage cellular hyperplasia.[17, 21] On X-ray examination, right-sided pleural effusion and/or pneumonitis is seen in up to one half of cases.[18, 19] Serum glutamic pyruvic and oxaloacetic transaminase values are elevated and parallel disease severity.[19] In severe cases prothrombin times are prolonged with deficiencies in factors 2, 5, 7, and 10.[17] Severely ill patients are hyponatremic and have fairly marked metabolic acidosis and ketonuria.[19] Hyperkalemia has been observed terminally.[18, 19]

Summarized briefly, dengue hemorrhagic fever has four distinguishing characteristics: 1) a period of fever for two or more days followed by rapid deterioration, 2) hepatomegaly, 3) shock, and 4) one or more abnormalities of the hemostatic mechanism.

While various pathologic findings have been described, some of these may be explained by inclusion of cases other than hemorrhagic fever owing

to the lack of etiologic identification.[22,23] Most autopsies show nonspecific capillary damage with resultant leakage of fluid, plasma, and erythrocytes from vessels into interstitial spaces and serosal cavities. In the reticuloendothelial system there is marked proliferation of lymphocytoid and plasmacytoid cells with marked increase in phagocytic activities. In the liver

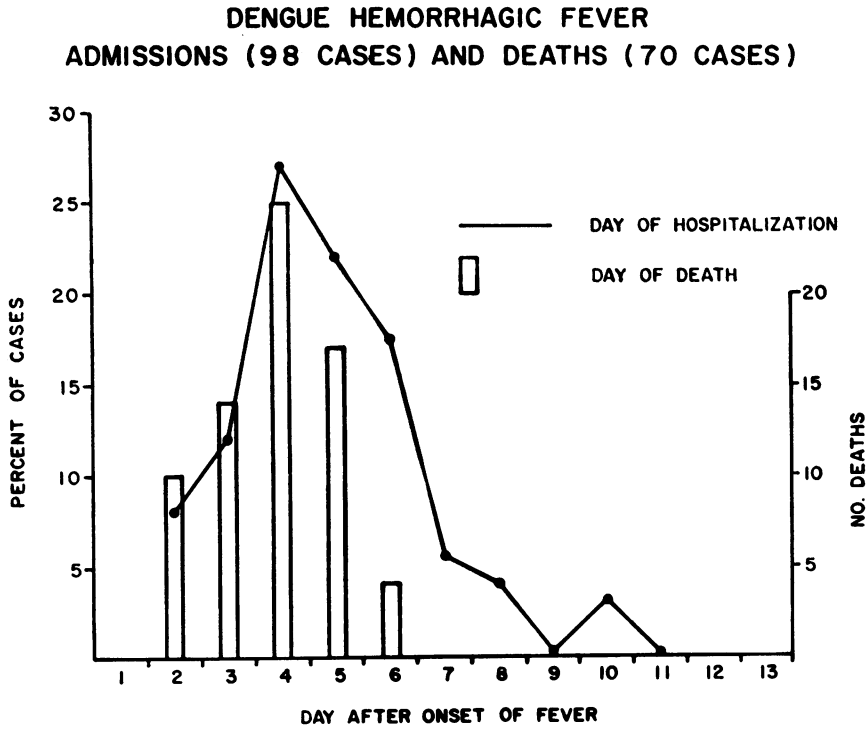

FIG. 2. Day of hospitalization and day of death in dengue hemorrhagic fever, Children's Hospital, Bangkok, 1962.[16]

there is focal hyaline or acidophilic necrosis of parenchymal and Kupffer cells and infiltration of portal areas and sinusoids by lymphoid cells. In a number of autopsies inclusions resembling Councilman bodies have been described.[21] Renal lesions except for minor hemorrhage are rare. Changes consistent with depletion of adrenal cortical cells are frequent. Adrenal cortical and pituitary hemorrhage is rare. Only occasionally was hemorrhage considered the possible cause of death. In these cases bleeding was either intracerebral or massive gastrointestinal hemorrhage. In most

patients pathognomonic gross or microscopic lesions and pathologic abnormalities sufficient to account for death could not be found.

Detailed clinical studies of hemorrhagic fever recently completed at the SEATO Thai Hemorrhagic Fever Study Center have resulted in the development of a proposed patho-physiologic sequence for dengue hemorrhagic fever:[19]

Following the bite of an infected mosquito dengue virus multiplies in one or more as yet unknown sites in the body. After an undetermined incubation

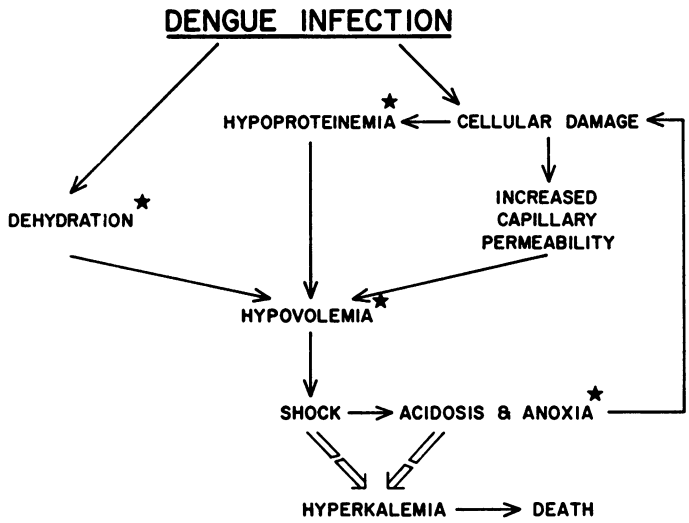

FIG. 3. Proposed pathophysiologic sequence in dengue hemorrhagic fever.[19]

period a febrile response ensues. Fever is followed in three or more days by capillary damage. This capillary damage is more severe than that which is probably a frequent accompaniment of many viral illnesses. The capillary damage of hemorrhagic fever is severe enough to allow first fluid, then protein to leak into extravascular spaces. In addition, there may be an associated primary hypoalbuminemia. The cumulative effect of dehydration, due to vomiting, fasting and thirsting, and this internal fluid loss results in hemoconcentration and hypovolemia. These in turn increase the work of the heart and cause tissue hypoxia. Tissue hypoxia and possibly other toxic infectious factors result in metabolic acidosis and hyponatremia. For reasons not known liver damage appears to exceed that of other major viscera. Progressive liver damage results in transaminase elevations and decreased production of blood clotting proteins. At this same time the patient becomes

thrombocytopenic, due in part, perhaps, to platelet sequestration on damaged endothelial surfaces and in part to the marked depression of platelet formation.

If the patient's physiologic abnormalities are not corrected by therapeutic intervention a cyclic sequence shown in Figure 3 may occur. Increasing metabolic acidosis and hypoxia lead to increased endothelial damage, increased fluid loss, decreased blood volume, more hypoxia and deeper shock. During this phase children are particularly prone to spontaneous gastrointestinal hemorrhage. This is also true of shock due to other causes.

TABLE 1. DENGUE VIRUSES ASSOCIATED WITH SEVERE HEMORRHAGIC FEVER OR DEATH. THAILAND, 1958-1962

		*Isolations of indicated virus type**			
Disease severity	*Series*	*D1*	*D2*	*D3*	*D4*
Hemorrhagic fever with shock and/or gastrointestinal hemorrhage	Hammon[26]		3/?		
	Dasaneyavaja[27]		3/61		
	Halstead[25]	2/74	8/74		
Death	Dasaneyavaja[27]				1/?
	Halstead[25]	1/72	3/72		

* Numerator indicates number of viruses isolated; denominator indicates total patients studied in category.

Even without this complication, however, shock, hypoxia, and metabolic acidosis alone may be severe enough to start an irreversible physiologic sequence that ends in death. Shown in the figure and marked with a star are the points in the cycle of death that may be responsive to treatment. Using only physiologic supportive therapy including oxygen and replacement of fluid and protein losses, many children have made satisfactory recovery.[19]

ETIOLOGIC AND VIROLOGIC STUDIES OF HEMORRHAGIC FEVER

At least 4 and perhaps 6 different types of dengue viruses have been isolated from patients with a febrile disease occurring during outbreaks in which at least some severely ill patients had the syndrome described above. This cautious statement is necessary and pertinent. Since pathophysiologic evidence is lacking that nonshock dengue infection in Asian children differs significantly from other undifferentiated viral illnesses or from classical dengue fever and since outbreaks are mixtures of disease syndromes, it is

not sufficient to merely associate virus and disease epidemiologically to establish the etiology of the hemorrhagic fever. Careful, repeated and prolonged etiologic studies of hemorrhagic fever are needed.

Although it has been proposed that dengue viruses recovered in Bangkok and resembling types 1 and 2 are sufficiently different antigenically to be named dengue 5 and 6[24] studies in Bangkok are not sufficiently complete to support or reject this contention. In this paper, viruses resembling type 1 and/or TH-Sman will be referred to as type 1; viruses resembling type 2 and/or TH-36 will be referred to as type 2.

Table 1 summarizes virus isolation by disease severity in Thailand from 1958-1962. As shown, 17 dengue type 2 viruses have thus far been associ-

TABLE 2. DENGUE VIRUSES RECOVERED FROM *Aedes aegypti* AND MILD AND SEVERE HUMAN ILLNESSES. BANGKOK, 1962-3[25]

Host	*Viruses isolated*			
	Dengue 1	*Dengue 2*	*Dengue 3*	*Dengue 4*
Aedes aegypti	5	6	7	2
Undifferentiated fevers	10	7	7	0
Hospitalized hemorrhagic fever	9	10	3	0

ated with severe disease and deaths. During this same period dengue types 1, 2, 3, and 4 viruses were circulating in Bangkok and causing human disease. Virus isolations during 1962-1963 from mosquitoes and mildly ill patients are shown in Table 2. Although the numbers are small, there is a suggestion that types 1 and 2 dengues are more frequently associated with hospitalized hemorrhagic fever patients while dengue 1, 2, and 3 were recovered with equal frequency from mosquitoes and mild dengue infections. It is of interest that the only dengue virus isolated from the Penang, South Vietnam, and Calcutta outbreaks was dengue type 2. Further, dengue 2 has been isolated from Singapore and the Philippines. Dengue 2, it seems, stands implicated in the etiology of severe dengue hemorrhagic fever. The status of other dengue types is less clear.

A discussion of data on the association of virus type and disease severity in hemorrhagic fever would not be complete without the presentation of two related observations.

First, the inability to recover any virus from the tissues of patients dying of hemorrhagic fever. During the past three years homogenates of 198 large viscera obtained from 46 patients dying of hemorrhagic fever have been tested in suckling mice. A blind passage technique was employed which

had been used successfully to recover nearly 300 dengue viruses from mosquito suspensions or human sera during the same period.[8] Not one dengue virus was recovered from these tissues, although three ether resistant viral agents, tentatively classified as coxsackie A viruses were recovered.

Recently, additional techniques have been used to try to detect dengue antigen or to "unmask" dengue virus in tissues. These have been: 1) tissue homogenates used as immunizing antigens, animals then bled and tested for dengue antibody or challenged intracerebrally with a lethal dose of

TABLE 3. RATE OF RECOVERY OF DENGUE VIRUSES FROM PERIPHERAL BLOOD OF PATIENTS WITH UNDIFFERENTIATED FEVER, AND HOSPITALIZED PATIENTS WITH HEMORRHAGIC FEVER SEROLOGICALLY CONFIRMED AS DENGUE INFECTION, AND FROM PATIENTS DYING OF HEMORRHAGIC FEVER[25]

Day of disease	*Mild dengue*	*Hemorrhagic fever*	*Deaths*
1	8/14* (57.1 per cent)	0/3 (0 per cent)	1/3 (33.3 per cent)
2	2/5 (40.0)	7/16 (43.8)	0/1 0
3	4/6 (66.6)	11/42 (26.2)	1/10 (10.0)
4	5/8 (62.5)	9/40 (21.4)	0/14 0
5	0/2 0	3/25 (12.0)	0/13 0
6	0	1/21 (4.7)	0/3 0
7		0/4 0	0/2 0
Total	19/35 (49.7 per cent)	31/151 (20.5 per cent)	2/46 (4.3 per cent)

* Number of isolates/patients studied.

weanling mouse adapted dengue virus; 2) cell cultures made of fresh liver tissue 3) tissue suspensions treated with genetron to attempt to break hypothetical antigen-antibody bonds, and 4) fresh frozen autopsy tissues stained with fluorescein conjugated dengue antibody.

None of these techniques has been successful. These studies may be explained by 1 of at least 2 hypotheses: 1) dengue virus does not multiply in tissues that show pathologic changes consistent with viral damage but multiplies in tissues as yet inadequately examined or 2) dengue virus multiplies in tissues examined but has disappeared at the time of death.

A second observation suggests that dengue virus disappears more rapidly from the blood of fatal cases than from milder dengue infections. Three groups of patients were studied: out-patients with a variety of mild undifferentiated febrile diseases, patients hospitalized with the diagnosis of hemorrhagic fever including shock and nonshock cases, and patients dying of hemorrhagic fever. The virus recovery rates from blood obtained on

various days of illness are shown in Table 3. If isolation rates on the same day after onset of fever are compared in each group, it will be noted that the rate of virus recovery is inverse to the disease severity.

EPIDEMIOLOGY OF DENGUE HEMORRHAGIC FEVER

Since first described, hemorrhagic fever outbreaks have been reported from both cities and villages in South and Southeast Asia. The disease has shown a tendency to be recurrent and to spread to adjacent areas. Epidemic mosquito borne hemorrhagic fever is a disease of the rainy season and of the period of *Aedes aegypti* abundance. However, in highly endemic areas such as Bangkok or in tropical areas without seasonal distribution of rainfall, cases may occur in every month of the year.

In Bangkok, the epidemic dissemination of dengue viruses follows the onset of the yearly monsoon and varies directly with the population of *Aedes aegypti* mosquitoes.[13,14] There are biannual epidemic surges. In 1958, 1960, 1962, and 1964 there were 2297, 1660, 4187, and 5358 hospitalized patients, respectively, while in 1959, 1961, and 1963 only 127, 452, and 1644 admissions for hemorrhagic fever were recorded.[13,25] It is speculative whether this epidemiologic phenomenon is related to the duration of heterologous immunity which follows a major outbreak or more simply to the development of a critical size population of susceptibles through births. House to house studies made in 1962-64 have shown that hemorrhagic fever appears to spread in what might be called a "brush fire" fashion. Areas hyperendemic one year become hypoendemic in the following year and *vice versa.* This pattern may be independent of total cases city-wide.[25]

Although Simmons and co-workers demonstrated that *Aedes albopictus* may transmit dengue viruses, there is no evidence from Thailand that this mosquito is of importance as a vector in urban areas.[28] The urban and suburban ecologic niche is firmly occupied by *Aedes aegypti* and *Aedes albopictus* is found only rarely. In Singapore and the Philippines, *Aedes albopictus* is more numerous in urban areas and it may be that this species does serve as a vector of dengue there.[11]

One of the most interesting epidemiologic phenomena observed in Thailand has been the absence of classical dengue fever accompanying outbreaks of hemorrhagic fever. As previously noted the conjunction of these two diseases has characterized the supposed earlier occurrences of hemorrhagic fever. While classical dengue fever occurs only rarely among the Thai and Chinese residents of Thailand, this syndrome does occur frequently among foreign residents infected with dengue virus. Altogether, approximately 150 cases of classic dengue fever have been confirmed

virologically in foreign residents of Thailand in 1962 through 1964 in our laboratory. Dengue viruses isolated from these persons are apparently identical to those recovered from Thai patients.

Little mention has been made up to this point of another important arthropod-borne virus illness occurring simultaneously with dengue hemorrhagic fever in several countries in Southeast Asia. The causative agent,

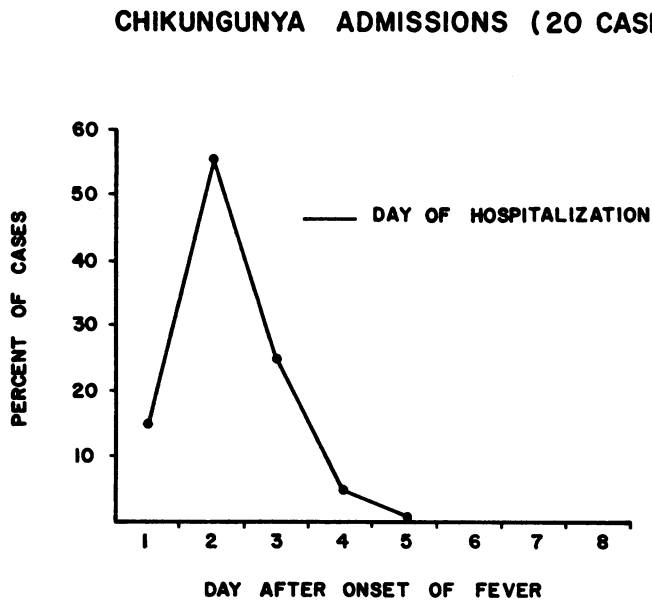

FIG. 4. Day of hospitalization of virologically confirmed chikungunya disease, Children's Hospital, Bangkok, 1962-3.[16]

chikungunya virus, belongs to Casals' group A and is closely related or identical to the virus causing human disease in eastern and central Africa.[20] In Africa, chikungunya virus is the cause of a dengue fever syndrome.[16] This virus also causes dengue fever in residents of South and Southeast Asia, particularly in areas where the virus is newly introduced such as in India during the 1963-1964 outbreaks.[10,21] In Thailand, chikungunya disease has been recognized principally in children. The day of hospitalization for 20 cases of chikungunya virus infections is summarized in Figure 4. As shown, chikungunya is an illness with abrupt onset in which maximum prostration occurs within the first two days after the onset of fever. A positive tourniquet test, rash, petechiae, and thrombocytopenia are common in chikungunya, however, hepatomegaly, severe bleeding, and shock

are rare (Table 4). Finally, chikungunya is a shorter illness than dengue hemorrhagic fever (Fig. 5). The usual chikungunya infection is readily distinguished from severe hemorrhagic fever, but the distinction between milder dengue infections and chikungunya may be impossible. In Thailand, chikungunya is no longer considered to be the cause of the severe hem-

TABLE 4. COMPARISON OF SELECTED CLINICAL FEATURES IN HOSPITALIZED THAI AND CHINESE CHILDREN WITH CHIKUNGUNYA AND DENGUE INFECTIONS (HEMORRHAGIC FEVER). BANGKOK, THAILAND, 1962-4[16, 25]

Finding	*Per cent occurrence of finding by etiology*	
	Chikungunya (20 cases)	*Dengue (98 cases)*
Positive tourniquet test	75 per cent	81 per cent
Petechiae	45	62
Epistaxis	10	17
Vomiting	60	63
Abdominal pain	45	50
Lymphadenomegaly	50	38
	Similar	
Purpura	0 per cent	20 per cent
Melena	0	12
Hematemesis	0	12
Hepatomegaly	15	48
Shock	0	35
Cool extremities	15	56
Cyanosis	5	27
Maculo-papular rash	50	13
Myalgia	55	10
	Different	

orrhagic fever syndrome but rather an acute febrile disease with occasional hemorrhagic manifestations and a good prognosis.

Evidence to date suggests that *Aedes aegypti* is the urban vector of chikungunya virus. Transmission from rodent to rodent with this species has been accomplished successfully.[32] In studies conducted in our laboratory this virus has been recovered 17 times from *Aedes aegypti* and only once from *Culex pipiens quinquefasciatus*.[25] Failure of chikungunya virus to survive in this latter species has been reported by several investigators.[32, 33] Although the urban epidemiologic cycle of chikungunya appears to be man to *Aedes aegypti* to man, there is evidence of the existence of a sylvan cycle possibly involving *Culex tritaeniorhynchus,* and large domestic animals. This supposition is based upon the recovery of chikungunya virus

from this mosquito species and the detection of neutralizing antibodies to chikungunya in a high percentage of pigs, water buffalo, and cattle resident on the Central Plain of Thailand.[25] Whether and under what circumstances any of these mammals can function as hosts for transmission of chikungunya virus to mosquitoes is not known.

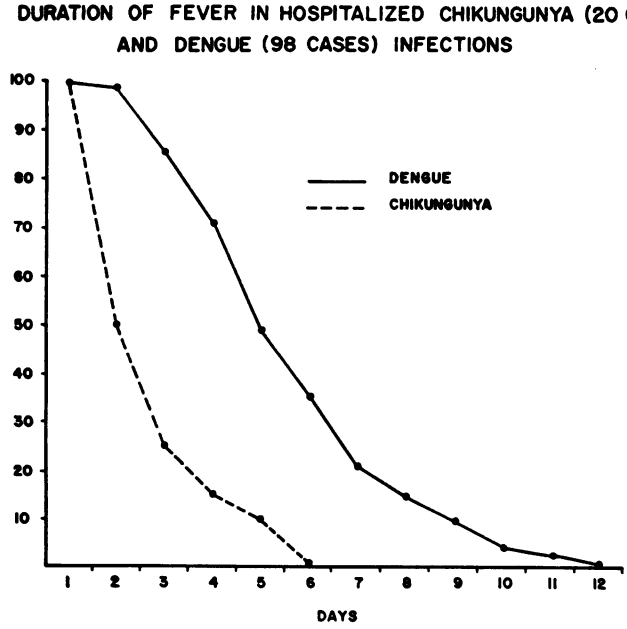

FIG. 5. Duration of fever in virologically confirmed hospitalized dengue and chikungunya infections. Children's Hospital, Bangkok, 1962-3.[16]

CONTROL

Although vaccination is a theoretical method of control of dengue and chikungunya epidemics, development of vaccine for these viruses has been slow. Since dengue viruses are generally considered to be poorly antigenic, current efforts center on attenuated live virus vaccine. Low mouse passage attenuated virus vaccines are available for dengue types 1 and 2.[84, 85] These vaccines have been shown to protect against homologous challenge and provide heterologous protection for several months. Experiments with multivalent vaccine and sequential parenteral vaccination with types 1 and 2 at six week intervals have failed to confer protection to both types.[84] Thus, vaccination with four different dengue virus types can be expected to be a long process as it will be necessary to wait until heterologous antibody dis-

appears to assure vaccine "takes." A living or killed virus vaccine for chikungunya virus would appear to present few of these difficulties.

In the absence of a suitable vaccine, vector control is the only method available to combat hemorrhagic fever. Areas that are *Aedes aegypti* infested but free of dengue or chikungunya viruses should implement quarantine procedures or case finding techniques for passengers arriving from hemorrhagic fever epidemic areas.

Permanent control of *Aedes aegypti* must combine public cooperation in reducing household breeding sites with provision of reliable piped water to all residences and the destruction of breeding sites outside houses. For the immediate future such measures must be supplemented by a carefully planned *Aedes aegypti* control program using insecticides against larvae and adults as well as the full range of public health measures. It is to be hoped that control measures will be instituted immediately in urban areas highly endemic for hemorrhagic fever to reduce transmission of viruses and thereby prevent the seeding of satellite outbreaks.

DISCUSSION

When dengue viruses were isolated from children with a severe and fatal disease in 1956, it was thought that a new dengue induced syndrome had appeared. In fact, this was probably not a new syndrome, but rather the first contemporary recognition of a disease initially described in 1897.

Dengue hemorrhagic fever as a clinical entity is quite distinct from dengue fever. Although some features of the two syndromes are similar, the differences are striking and the occurrence of shock in hemorrhagic fever clearly differentiates the two. Thus, classical dengue fever occurs primarily in adults and is characterized by myalgia, arthralgia or bone pain, and leukopenia, but only rarely by hemorrhage, vomiting, and liver enlargement. Death is extremely rare. On the other hand, dengue hemorrhagic fever is a childhood disease frequently associated with a hemorrhagic diathesis, vomiting, and a palpable liver. Myalgia, arthralgia, bone pain, and leukopenia are rare. Shock occurs in up to 40 per cent of hospitalized cases and deaths are common. While both syndromes are associated with dengue infection and there is considerable overlap in clinical features, the classical syndromes of each are distinct.

Although shock is a terminal event in severe infections with many bacteria or viruses, the hypotension that occurs with dengue infections in South and Southeast Asia is unusual in that shock clearly precedes death by hours or days. Furthermore, in a number of instances it may respond to treatment. Hare's comparison of dengue shock syndrome to cholera[1] was

most apt, since the physiologic antecedents in both are similar. However, the dengue patient loses his fluids internally, thus complicating therapy. During the recovery phase all of this fluid will be reabsorbed and patients may develop hypervolemia and heart failure. At present, the pathophysiologic sequence of dengue hemorrhagic fever appears to be unique among virus diseases.

The factors that contribute to the pathogenesis of hemorrhagic fever remain obscure. Side by side infections of Caucasians and Asians suggest that the same dengue viruses are capable of producing both syndromes. There are several possible explanations for the occurrence of two distinct syndromes caused by the same virus. These involve both the agent and the human host.

Virus. 1) it is possible that simultaneous infections with more than one infectious agent alters the disease syndrome produced by dengue viruses in Southeast Asia. There is serological evidence of simultaneous infection with dengue and chikungunya in a small percentage of hemorrhagic fever cases.[24, 25] However, there is no increased incidence of shock and death among children with combined virus infection. Indeed, these children appear to develop a syndrome that varies as widely as the one caused by dengue alone. The possibility that infection with other, as yet unidentified, viral agents might affect the expression of dengue infection has not been evaluated.

2) The infecting dose of virus might influence the severity of the resultant disease in human dengue. There is no evidence to suggest that the infectious dose is important in the pathogenesis of hemorrhagic fever.

3) When dengue viruses are successively passed through mice in a brief period of time, they become more virulent and cause paralysis and death in most of the animals inoculated with late passages. This altered virulence is then a permanent characteristic of the virus. The mutant is referred to as a "mouse-adapted" strain.

In Southeast Asia there is year-round transmission of arboviruses; dengue strains probably survive for many years. Might a prolonged human epidemic be a natural counterpart of rapid passage experiments? It may be that more virulent "man-adapted" dengue strains are responsible for the change in the clinical picture caused by infection. It is of interest that severe disease in the Australian and Greek epidemics appeared after at least two consecutive dengue epidemics.[1, 3, 4] Consecutive dengue outbreaks are relatively rare. Most large dengue outbreaks have been nonrecurrent, the virus being eliminated, perhaps, with the vector as cold weather occurs. *A priori* it seems unlikely that simultaneous mutation of several dengue types would

occur. Therefore, a test of the mutation theory might be the number of dengue virus types that cause severe disease. At present, evidence suggests the importance of dengue 2 virus. However, a final decision on causative agent or agents cannot be reached until more hemorrhagic fever cases are studied and until laboratory techniques allow reproducible discrimination of strain and type variations within the dengue complex.

Host. Host reaction can also influence the clinical course of an infectious disease. Nutrition, heredity, hypersensitivity and degree of immunity may be determinants of the course of disease and might explain different responses to dengue infection.

1) While there are no pertinent nutritional studies, there are also no data which incriminate poor nutrition as the basis for hemorrhagic fever. Hemorrhagic fever occurs among all classes and socioeconomic groups in Bangkok.[25] No gross evidence of nutritional deficiency has been reported among patients with this disease.[25] If subclinical nutritional deficiency states produce a favorable environment for hemorrhagic fever to develop, one might expect cases among the elderly, a group that has been spared in the recent epidemics.

2) As yet there are no data with which to evaluate possible heredofamilial factors in hemorrhagic fever.

3) Most hemorrhagic fever patients demonstrate a secondary type of antibody reaction to group B arbovirus antigens. A hyperimmune reaction in persons previously sensitized to dengue antigens may therefore be postulated as an underlying mechanism in the pathogenesis of hemorrhagic fever. On the other hand, if prior dengue virus exposure was a significant pathogenic factor, one might expect a higher incidence of hemorrhagic fever among adults than is presently seen. One small outbreak has occurred in an area where dengue had not been epidemic for several years and children, some with typical hemorrhagic fever with shock, demonstrated a primary group B antibody response.[14]

4) Racial or ethnic differences may determine susceptibility to hemorrhagic fever. Although diverse peoples have been affected in India, the Indochinese peninsula and the Philippines, no natives of Western countries have developed hemorrhagic fever with shock during a series of epidemics. More data are needed to evaluate this possible racially determined difference in reactivity to dengue infection.

It is clear that no definitive statement can be made regarding the specific etiology or viral pathogenesis of hemorrhagic fever at present. It may be, however, that a combination of viral and host factors is responsible for the syndrome rather than only a single factor. It is hoped that this preliminary

report of studies undertaken in Thailand will stimulate wider interest in this challenging disease problem and lead to efforts that will clarify the present state of confusion.

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DISCUSSION: MAX THEILER*

The findings of Dr. Halstead and his associates in their studies of dengue infections in Thailand once again point up the fact that quite similar clinical syndromes can be caused by completely unrelated arthropod-borne viruses. I refer here to the clinical picture produced by infections with the chikungunya virus on the one hand and the various types of dengues on the other. Chikungunya is a member of group A and is antigenically completely distinct from the four types of dengue which are members of group B. Both of these agents infect man and in urban areas are transmitted by the mosquito *Aedes egypti*. Epidemics due to both agents may occur in a city at the same time. This has happened not only in Bangkok but also in Calcutta.

* Professor of Epidemiology and Microbiology, Yale University School of Medicine.