**   WHO Consultant on Dengue Hemorrhagic Fever, Children Hospital, Bangkok, Thailand

Dengue Hemorrhagic Fever: Problems and Progress *

by

SUCHITRA NIMMANNITYA **

Abstract

The paper represents a clinical reappraisal of dengue hemorrhagic fever (DHF) and the author's purpose to briefly review and discuss the pertinent data obtained to date. The most frightening picture of DHF that clearly differentiates this new clinical entity from the classical dengue illness and contribute to its cause of death is the shock syndrome.

The major pathophysiologic change that leads to hypovolemia and subsequent shock is the leakage of plasma. The acute onset of shock and the rapid, often dramatic clinical recovery when treated, together with the fact that no destructive or inflammatory vascular lesion has been observed suggested a functional vascular permeability change possibly due to a short acting pharmacological mediator.

Epidemiological and serological observations circumstantiated a hypothesis that DHF occurs as a result of a second infection with a heterologous dengue virus. Recent studies strongly implicated an immunological mechanism involving activation of complement system and its products, complement-derived anaphylatoxins as responsible for the initiation of shock. The findings of low fibrinogen and appearance of fibrinogen split product in correlation to the disease severity together with the constantly found thrombocytopenia indicated occurence of consumptive coagulopathy but probably not a major pathogenic role. The fact that in most cases, early and effective replacement of plasma volume results in favourable outcome, and that significant bleedings when present, usually occur after the onset of shock, and support to the major pathogenic role of the increased vascular permeability and extravasation of plasma.

The year 1956 was important in the history of dengue and perhaps in the history of viral diseases in general for it marked the first recognition of dengue hemorrhagic fever (DHF), a new urban disease of children characterized by fever, hemorrhagic diathesis, hepatomegaly and a life threatening shock syndrome. After the first epidemic in Manila the disease has spread to other countries in the Southeast Asia and the Western Pacific regions where Aedes aegypti mosquitoes (a dengue vector) are abundant.

In some of these areas during DHF outbreaks chikungunya virus, also transmitted by Ae. aegypti, sometimes caused similar but milder disease, more like classical dengue fever (Nimmannitya et al., 1969). Only dengue viruses are responsible for the severe life threatening diseases which is now considered as of significance among communicable diseases in most tropical Asian countries. The repetition of outbreaks or their extension to new areas have raised during the past two decades a number of public health problems which are complicated, difficult and not yet completely solved.

DHF is considerably a new disease or a new variant of dengue infection because of its unusual hemorrhages and the shock syndrome so-called dengue shock syndrome (DSS) which has been known for more than a century in Asia are largely age dependent, the disease is mild in children and more severe in adults. Infants and young children with dengue infection have syndrome ranging from undifferentiated fever to mild febrile illness sometimes with the triad of high fever, pain in various parts of the body and rash. The disease is known as non-fatal, death is rather an exceptional. DHF on the contrary, attacks mostly children under age 14 years and caused significant mortality among preschool age children of Southeast Asia and the Western Pacific regions where classical dengue syndrome is a rare incidence among indigenous people.

During the past two decades several research approaches have produced information which contributed to our present understanding of epidemiology, virology, immunology and clinical research. In each of these fields, there are significant unanswered questions remaining to be further pursued. In the point of view that some of the existing problems can be solved by appropriate action in applying the knowledges we already possess, it is my purpose to briefly review and discuss the pertinent data obtained to date on some aspects of DHF.

Virological and Epidemiological Aspects

The four dengue viruses form a subgroup of the group B arbovirus based on close antigenic relationships due to common or cross-reacting antigenic determinants present in
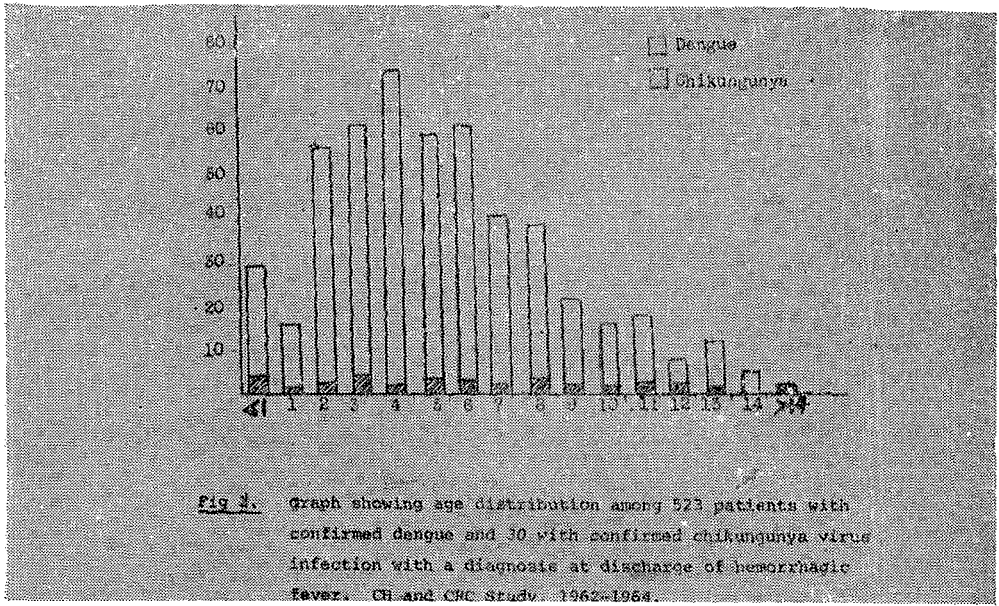
FIG. 1 : *Graph showing age distribution.*

Fig. 1. Graph showing age distribution among 523 patients with confirmed dengue and 30 with confirmed chikungunya virus infection with a diagnosis at discharge of hemorrhagic fever. CH and CMC Study, 1962-1964.
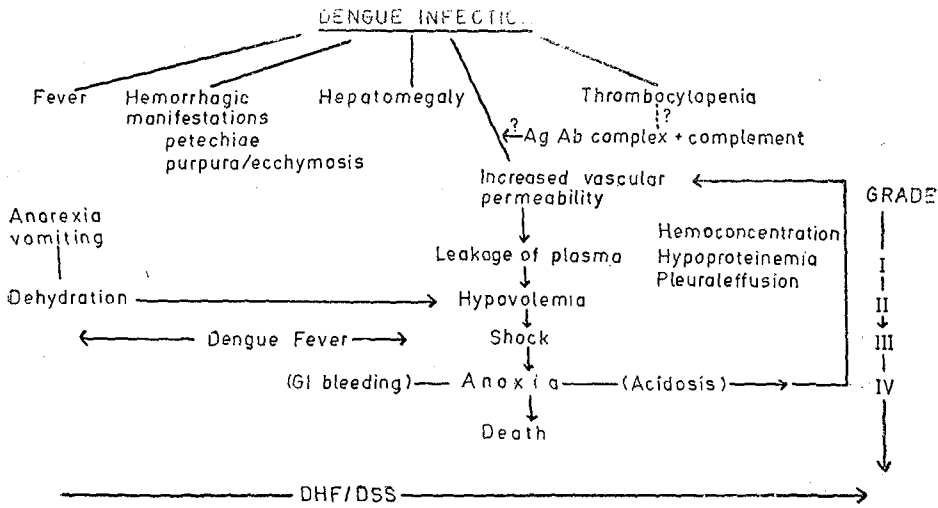
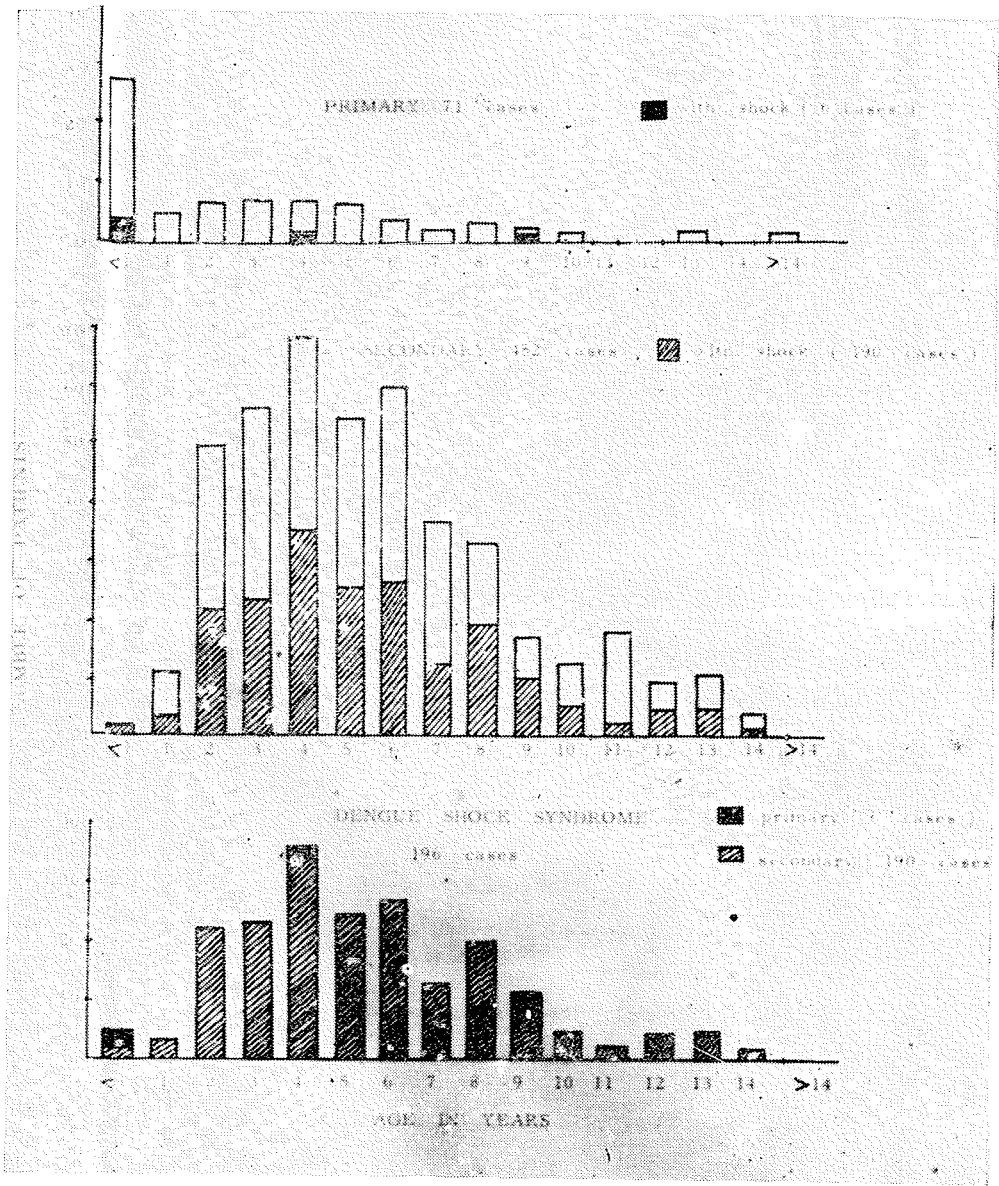FIG. 3 : *The Spectrum of Dengue Diseases.*

FIG. 2 : *Age distribution and accurence of shock in patients with primary and secondary dengue antibody response and in 452 DHF patients a secondary dengue antibody response. (Modified from Halsteed Nimmannitya, & Cohen).*

complaint shortly before onset of shock.

Shock is characterized by a rapid and weak pulse with narrowing of the pulse pressure (20 mm. Hg. or less, regardless of the pressure levels, e.g. 100/90 mm. Hg.) or hypotension, with cold, clammy skin and restlessness, the onset of shock is usually abrupt and often profound. The patients are in danger of dying if appropriate treatment is not promptly given. The duration of shock is short, the patient may die within 12 - 24 hours or recover rapidly following appropriate antishock therapy. Prolonged uncontrolled shock may give rise to a more complicated course with metabolic acidosis, severe gastrointestinal hemorrhage and a poor prognosis.

Thrombocytopenia and concurrent hemoconcentration are constant findings. A platelet count of below 100,000/mm³ is usually found between the third and eight days, the platelet count falls and hematocrit rises before onset of shock.

The clinical diagnosis based on four major clinical manifestations:

a. fever, high continuous for 2 - 7 days.

b. hemorrhagic manifestations including at least a positive tourniquet test with any other.

c. hepatomegaly.

d. circulatory disturbances — in the form of shock in severe cases. And the two constant laboratory

findings thrombocytopenia and concurrent hemoconcentration provide the basis for accurate and rapid diagnosis before shock or irreversible shock occurred.

The spectrum of DHF/DSS is classified according to disease severity into four grades (Nimmannitya et al., 1969).

Grade I. Fever accompanied by non-specific constitutional symptoms, the only hemorrhagic manifestation is a positive tourniquet test.

Grade II. The additional manifestation to those of grade I is spontaneous bleeding, skin and/or other hemorrhages.

Grade III. Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mm. Hg. or less) or hypotension, with the presence of cold clammy skin and restlessness.

Grade IV. Profound shock with undetectable blood pressure and pulse.

Table I shows the occurence of major manifestations and laboratory findings in relation to disease severity. The presence of thrombocytopenia with concurrent hemoconcentration will differentiate grade I and II, non shock cases of DHF from classical dengue fever, and from other viral infections.

Pathophysiology

Vascular permeability

The major pathophysiological abnormality seen in DHF/DSS is an

acute increase in vascular permeability that leads to leakage of plasma. Plasma volume studies revealed a reduction of more than 20% in severe cases (Suwanik et al., 1967) supporting evidence of plasma leakage, include hemoconcentration, hypoproteinemia, serous effusion found at postmortem, and pleural effusion found on X-rays.

In severe cases, the onset of shock is acute, hematocrit rises sharply as plasma escapes through the endothelium. Hypovolemic shock, as a consequence of critical plasma loss leads to tissue anoxia, metabolic acidosis and death if uncorrected.

In most cases, early and effective replacement of lost plasma with plasma, plasma expander and/or fluid and electrolyte solution results in a favourable outcome. The acute onset of shock, and the rapid, often dramatic clinical recovery, together with the fact that no destructive or inflammatory vascular lesions are observed (Bhamarapravati et al., 1966) suggest transient functional vascular changes possibly due to a short acting pharmacological mediator (Russel, 1970).

Electrolyte disturbance frequently found and is considerably significant in the treatment is hyponatremia. This can be attributed to salt depletion in excess of water; salt depletion may have been present to some degree due to reduced salt intake from anorexia and increased loss from vomiting and excessive sweating, water retention is the result of both decreased renal excretion and increased oxidative water formation from increased metabolism during the febrile stage. Few cases have evidences suggesting inappropriate ADH secretion (Varavithya et al., 1973).

Early in the course of illness respiratory alkalosis with mild metabolic acidosis may be found, but in the cases with prolonged uncontrolled shock metabolic acidosis is more common and may cause a more complicated course if not corrected.

Hemollhagic Diathesis

Bleeding manifestations in DHF range from mild skin hemorrhage as positive tourniquet test and petechiae, epistaxis, gum bleeding, to the severe sometimes fatal-massive gastrointestinal hemorrhages.

Hematologic changes in DHF

1. Vasculopathy

— Capillary fragility changes result in positive tourniquet test.
— Capillary response to injury is poor as manifested by the prolonged bleeding time.

2. Thrombocytopenia

Thrombocytopenia is a constant finding in DHF. Platelet counts fall to a moderately or markedly low level by day 3, usually preceeding shock in severe cases and rise to normal or sometimes supernormal level by day 8 to 10. It is important

to note that although the level of low platelet counts is in correlation with the disease severity, the very low level of platelets (below 40,000 per cu. mm.) is not always correlated with severe bleeding. The reverse, however, is always true, i.e. in cases with severe hemorrhage the platelet counts are always very low.

Bone marrow studies in these patients indicated hypocellular and decreased number of megakaryocytes suggesting decreased production during the early febrile phase. This is probably one factor — a minor one — in explaining thrombocytopenia in DHF (WHO, 1966).

The rapid fall of platelet counts to a very low level points to a destructive process or sequestration as a more important role. The platelets survival studies in some of these patients revealed an unusual shortage of its half life implicating enhanced destruction of the circulating platelets (Mitrakul, 1973). A consumptive coagulopathy is one possibility, but is not absolute evidence of platelets destruction, just as a low platelet count is no proof of intravascular coagulation.

The observation of sudden drop of platelets concurently with hemoconcentration preceeding shock as shown in Fig. 4, occurred simultaneously with the rising antidengue antibody suggests another possibility that platelets may be aggregated or adhered to antigen antibody complex.

3. Coagulopathy

Table 2 shows the results of fibrinogen, fibrin degradation product (FDP) and platelets in correlation to the disease severity. The low level of fibrinogen and the presence of FDP together with the constantly found thrombocytopenia could be interpreted as evidence of disseminated intravascular coagulation (DIC). (WHO, 1973).

The screening coagulogram in some of these patients with high FDP level revealed prolonged partial thromboplastin time (PTT) in 54.6%, prolonged prothrombin time (PT) in 33.3% and normal thrombin time. These findings together with the observation that FDP is not always found in severe cases, and when present, the level is rather low, particularly if compared to the level found in classical DIC due to gram negative septicemia (Suvatte et al., 1973), suggest that mild consumptive coagulopathy may take place in DHF but no frank DIC which plays a significant pathogenetic role.

The assay of clotting factors revealed mild to moderate reduction of factors II, V, VII, IX, X (Weiss and Halstead, 1965; WHO, 1966) and also factor XII (Mitrakul, 1973; Edelman et al., 1973), in severe cases with shock while the non shock cases always showed normal coagulograms. In case of shock with severe bleeding there was a definite reduction in all coagulation factors except

factor VIII. The normal level of factor VIII, although no absolute evidence against intravascular coagulation, does, however, cast some doubt on the occurrence of consumptive coagulopathy in DHF.

It should also be noted that hepatomegaly is a constant finding in DHF, and that the liver function profile showed mild to moderate elevation of serum transaminases; at post mortem there were always changes indicating some degree of liver damage. It is quite possible that in severe cases of DHF, a certain degree of liver involvement may cause coagulation defects.

It thus appears that skin bleeding in DHF in general is due to capillary factors and thrombocytopenia in some extent. The gross massive bleeding is possibly due to more complex mechanisms; thrombocytopenia, coagulation defects, and probably in some extent due to consumptive coagulopathy particularly in those who have been in prolonged uncontrolled shock with complicated metabolic acidosis. Further information is needed on the role of shock per se in causing or potentiating DIC.

Pathogenesis

The association of secondary infections and the consequent anamnestic antibody response with DHF is firmly established. This indicates that an immunological mechanism is involved. The complement studies carried out in recent years have greatly clarified the pathogenetic mechanisms in DHF and DSS. The important central role of complement activation and the consumption of C3 have been conclusively demonstrated (WHO, 1973; Bokisch et al., 1963).

The occurrence of immune complexes is presumed on the basis of simultaneous presence of virus and antibody in patient's serum, and this is supported by evidence of C1 consumption and the finding of IgG, dengue antigen, and C3 deposited in kidneys of patients convalescent from DHF (Futrakul et al., 1973).

Recent studies revealed that immunological enhancement of dengue virus replication in peripheral leukocytes in the sense that viremia in secondary infection is quantitatively greater than viremia in primary infection (Marchettee, 1974). These findings suggest that cell mediated immunity may also be involved in the pathogenetic mechanism of DHF. In secondary infection with enhanced virus replication, and the rapid rise to a high level of antidengue IgG antibody the interaction to form immune complex is more feasible and become significant.

Fig. 5 shows the complement profiles of DHF patients (WHO, 1973), complement depression in DHF involved primarily C3, C3 preactivator (C3PA), C4, and C5. The marked depression of serum level of comple

ment was found to be correlated with the severity of the disease.

The activation of C3 and C5 is accompanied by dissociation of low molecular weight peptides called C3a and C5a anaphylatoxins which are very potent permeability increasing factor and have the capability to release histamine (Muller - Eberhard and Vollota, 1971). Since the C3 concentration was reduced by at least 33% in the shock patients and a reduction of 33% in the C5 levels also occurred in 89% of such patients, it may be that large amounts of anaphylatoxin are liberated during the shock phase. Although plasma contains a powerful inactivator of the two peptides (Bokisch and Muller Eberhard, 1971), it is quite possible that these peptides contribute to the development of shock before they undergo inactivations (WHO, 1973). The fact that anaphylatoxin is rapidly inactivated and eliminated from the circulation is in accordance with the short period and often dramatic recovery of shock when treated.

The question of a possible role of bradykinin in causing permeability increase and hypovolemia has been clarified in the recent studies which showed no significant change of bradykinin or kallikrein inhibitor in relation to the disease severity. This negative finding in kinin study together with the evidence of rapid fall of C3 preceeding shock, during shock and the return to nor-

mal in convalescence observed in the same studies give strong support to the central role of complement activation in the pathogenesis of DHF (Edelman et al., 1973).

The complement has been shown to be capable of initiating blood coagulation through the platelets (Zimmerman and Muller-Eberhard, 1971).

It is quite possible that the mild consumptive coagulopathy observed in DHF is a consequence of complement activation occurring during its intermediate pathway and probably does not play a major pathogenic role. This is supported by the fact that significant bleeding is infrequent in DHF, when present usually occurs after the onset of shock, after a prolonged uncontrolled shock.

The evidences that in most cases early and effective replacement of plasma volume results in favourable outcome and that with early treatment of shock the incidence of severe bleeding is further reduced, strongly indicate the major role of the increased vascular permeability and extravasation of plasma, in the pathogenesis of DHF/DSS.

Treatment

As in other viral infections there is no specific antiviral agent for dengue infection. Symptomatic and supportive measures are, however, effective in DHF and DSS providing prompt and appropriate antishock

therapy is given before irreversible shock takes place.

DSS is a hypovolemic shock due to leakage of plasma, hyponatremia is commonly found, thus immediate administration of intravenous fluid to expand plasma volume is most essential. Serial hematocrit determinations are most essential guide in therapy since they reflect the degree of plasma leakage and the need for intravenous fluid therapy. Hemoconcentration usually precedes blood pressure and pulse changes. Moreover the hematocrit is also a good indication for stopping the intravenous fluid when the reabsorption of the extravasated plasma takes place.

The experience in the management of shock in DHF at the Children's Hospital, Bangkok, has proved satisfactorily with the following regimens:

1. Immediate replacement of the existing plasma loss with plasma or plasma expander, and/or isotonic salt solution.

2. Correction of further plasma loss and maintaining of circulating volume for another 12 to 24 hours or at the most 48 hours.

3. Correction of electrolyte disturbance and/or acid base imbalance.

4. Fresh blood transfusion in case of massive bleeding.

The steadily decline in mortality rate after 1964 without using steroids (Fig. 6) precludes the necessity of this drug in the therapy of DHF/DSS. Early recognition of cases as well as early and appropriate treatment of shock with proper monitoring of the patient's conditions play important roles in the reduced mortality rate from 9% in 1964 to 2% in 1973.

A controlled study comparing the results of treatment of DSS with and without steroids showed no difference between the two methods (Pongpanich et al., 1973). The most recent blood cortisol level studies in DHF patients showed high cortisol level during the stage of shock. The level in shock cases is 4 to 5 times higher than in control (Tuchinda et al., 1974). This could be simply interpreted as no evidence of adrenal insufficiency. Nonetheless the possibility of harm effect of the high cortisol levels seen in the severe cases should not be overlooked. A further investigation is needed.

In conclusion, in spite of the many questions and puzzles that remain, body of knowledges in various aspects of DHF has compiled. Better understanding of the disease improves clinical diagnosis and management of DHF, and the mortality rate reduces. Good and accurate clinical criteria for diagnosis reduce the problem of overdiagnosis and a great demand of hospital beds. Early recognition of cases is also important in surveillance program of DHF, and for the control program.

In view of the fact that there is no vaccine available, the fundamental measure to be taken in the disease prevention and control is to control the vector mosquitoes. To achieve the goal in DHF control there is a need for close cooperation among all concerned. A surveillance program for DHF at the international as well as at local levels is most desirable. Logistics of the operation and research on various aspects of DHF may vary from one country to another. However, the experiences gained in one country may interest the others.

REFERENCES

1. BHAMARAPRAVATI, N., BOONYA-PAKNAVIK, V., and NIMSOMBURA-NA, P. : Pathology of Thai hemorrhagic fever. An autopsy study. Bull. WHO 35 : 47-48 (1966).

2. BOKISCH, V.A. and MULLER-EBERHARD, H.J. : J. Clinical Invest. 49 : 2427-2436 (1971).

3. BOKISCH, V.A., TOP, F.H. PONGPA-NICH, B., PANCHAPAKARN, P. and NIMMANNITYA, S. : Catabolic rate of C3 and C1 complement in dengue hemorrhagic fever patients (1972-1973). The SEATO Medical Research Lab., Bangkok, The Annual Progress Report (1973).

4. EDELMAN, R., NIMMANNITYA, S., COLMAN, R. W. TALMO, R. C. and TOP, F.H. : Evaluation of plasma kynin system in dengue hemorrhagic fever (in press, 1973).

5. FISCHER, D. B. and HALSTEAD, S. B. : Observations related to the pathogenesis of dengue hemorrhagic fever. Examination of age specific sequential infection rate using a mathematical model. Yale J. Biol Med. 42 : 329 (1970).

6. FUTRAKUL, P. et al. : Renal involvement and reticuloendothelial-system clearance in dengue hemorrhagic fever. J. med. Ass. Thailand 56 : 33-39 (1973).

7. HALSTEAD, S. B., NIMMANNITYA, S. and OHEN, S.N., : Observation related to a pathogenesis of DHF. Yale J. Biol. Med. 42 : 311-328 (970).

8. HALSTEAD, S. B., NIMMANNITYA, S. YAMARAT, C. and RUSSEL, P.K. : Hemorrhagic fever in Thailand. Newer knowledge regarding etiology. Jap. J. Med. Sci. Biol. 20 : 96-103 (1967).

9. IN : REPORT OF AN INTERNATIONAL COLLABORATIVE STUDY: Pathogenetic mechanisms in DHF. Bull. W.H.O. 48 : 117-133 (1973).

10. IN : WHO INTERREGIONAL SEMINAR ON MOSQUITO-BORNE HEMORRHAGIC FEVER OF SOUTH AND SOUTH-EAST ASIA. Bull. W.-H.O. 35 (1966).

11. MARCHETTE, N.J. : Immune enhancement of dengue virus replication in peripheral leucocytes — a possible mechanism in the pathogenesis of dengue shock syndrome. In : paper presented at the 13th SEAMO-TROPMED Seminar, Saigon (1974).

12. MITRAKUL, C. : Hematologic aspects in DHF. Chulalongkorn med. J. Thailand 17 : 203-207 (1973).

13. MULLER-EBERHARD, H.J. and VOL-LOTTA, E.R. : Formation and inactivation of anaphylotoxins. In : Proceedings of the 2nd Int. Symp. on the Biochemistry of the acute allergic Reaction. Quoted in Bull. W.H.O. 48 : 131 (1973).

14. NIMMANNITYA, S., HALSTEAD, S.B., COHEN, S.B. and MARGIOTTA, M.R. : Dengue and chikungunya virus infection in man in Thailand, 1962-1964. Amer. J. trop. Med. Hyg. 18 : 954-971 (1969).

15. PONGPANICH, B., BHANCHET, P., PANICHAYAKARN, P. and VALYA-SEVI, A. : Studies on DHF; clinical study, an evaluation of steroids as a treatment. J. med. Ass. Thailand, 56 : 6-14 (1973).

16. RUSSEL, P.K. : Pathogenesis of dengue shock syndrome : evidence for immunological mechanism. In Proc.6th int. Symp. on Immunopathology pp. 426-435 (Grindelwald, Basel Schwabe, Switzerland 1970).

17. RUSSEL, P.K. and NISALAK, A. : Dengue virus identification by the plaque reduction neutralization test. J. Immunol. 99 : 291 (1967).

18. SABIN, A.B. : Research on Dengue during World War II. Amer. J. trop. Med. 1 : 30 (1952).

19. SUVATTE, V. et al : Studies en serum complement C3 and fibrin degradation products in Thai Hemorrhagic fever. J. med. Ass. Thailand 56 : 24-32 (1973).

20. SUWANIK. R, et al : Plasma volume and other fluid spaces studies in Thai H.F.J. med. Ass. Thailand, 50 : 48-66 (1967).

21. TUCHINDA, C., VISUTAKUL, P., ANGSUSINGHA, K. and PUNNA-KANTA, L. : Blood cortisol level in Thai hemorrhagic fever. In preparation (1974).

22. VARAVITHLA. W. et al : Studies on DHF; Electrolyte Study. J. med. Ass. Thailand 56 : 15-23 (1973).

23. WEISS, H.J. and HALSTEAD, S.B.: Studies of hemostasis in Thai hemorrhagic fever. J. Pediat. 66 : 918-926 (1965).

24. WHITEHEAD, R.H., CHICUMPA, V. OLSON, L.C. and RUSSEL, P.K. : Sequential dengue virus infections in the white-handed gibbon. Amer. J. trop. Med. Hyg. 19 : 94 (1970).

25. WINTER, P.E. et al : Recurrenre of epidemic DHF in in an insular setting. Amer. J. trop. Med. Hyg. 18 : 573 (1969).

26. ZIMMERMAN, T.S. and MULLER-EBERMARD, H.J. : J. exp. Med. 134. 1601-1607 (1971). Quoted in Bull. W. H.O. 48 : 131 (1973).