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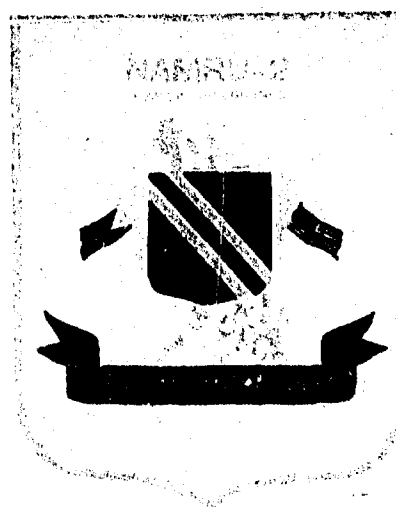
Curtis G. Hayes, Corazon R. Manaloto, Alicia Gonzales
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DENGUE INFECTIONS IN THE PHILIPPINES: CLINICAL AND VIROLOGICAL FINDINGS IN 517 HOSPITALIZED PATIENTS

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Abstract. From May 1983 to January 1984, 517 patients with laboratory confirmed dengue were studied at a hospital in Manila. Secondary dengue infections were diagnosed in 78% of these cases. Peak admission (28%) occurred towards the end of the rainy season in November. Most patients (78%) were <15 years old but only 3 were infants. Although some type of hemorrhagic finding occurred in 460 cases (89%), only 110 were classified as dengue hemorrhagic fever and the remainder as dengue fever with hemorrhagic manifestations. The clinical course was usually mild. Gastrointestinal bleeding was present in 65 cases, but only 2 patients developed shock. No fatalities occurred.

Dengue 2 was the predominant serotype with 53 isolates, followed by dengue 1 with 48 isolates, dengue 3 with 39 isolates, and dengue 4 with only 8 isolates. Dengue 2 was the only serotype with more isolates from sera with a homologous HI antibody titer >1:20 (57%) than from sera with a homologous HI titer ≤1:20 (43%). In contrast, most of the dengue 1 isolates (63%) were from sera with a homologous HI antibody titer <1:10, and this serotype was strongly associated with primary infections.

This study shows that dengue infections remain an important cause of pediatric hospitalization in the Philippines; however, the occurrence of life-threatening dengue hemorrhagic fever as has been described in several other large urban areas of Southeast Asia appears to be rare.

The first association of dengue (DEN) viruses with an outbreak of hemorrhagic fever was reported from Manila in 1956.^{1,2} During that outbreak, DEN-3 was most commonly isolated but 2 and 4 were also recorded (these represent the original isolates of serotypes 3 and 4). Diagnostic rises in antibody titer to DEN viruses also were found in hemorrhagic fever patients.

Since 1956 hospitalized cases of hemorrhagic fever continue to be reported each year in the Philippines, but most cases are only diagnosed clinically. In 1966, however, serology and virus culture were performed on 408 hospitalized patients during the largest recorded outbreak of dengue hemorrhagic fever (DHF) in Manila, and 217 (53%) were classified as having positive or presumptive DEN virus infections.³ As in 1956, DEN serotypes 2, 3, and 4 were isolated with type 3 predominating.

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No subsequent well described epidemic of hemorrhagic fever in the Philippines has been published. In the present report, we present clinical and virological studies conducted during a 1983-1984 outbreak of DEN in Manila.

MATERIALS AND METHODS

Patient selection and clinical studies

The study was performed at San Lazaro Hospital (SLH), Manila, the Philippine government's major infectious disease hospital. Between May 1983 and January 1984, all patients admitted to the Hemorrhagic Fever Pavilion of SLH were enrolled. The admitting diagnosis was made by the hospital staff physicians. No attempt was made to influence the criteria they used, which consisted primarily of acute fever with the presence of any bleeding manifestation.

After admission, information on the patient's personal background, history of illness, and the results of the initial physical examination, usually conducted by one of us, was recorded on

standardized code sheets. The patient's vital signs and other signs and symptoms, particularly in reference to bleeding and shock, were recorded on the same form each day during the course of hospitalization. Blood pressure was recorded twice daily, during the morning and afternoon, using a pediatric cuff for children. The tourniquet test to measure capillary fragility was performed by inflating the blood pressure cuff to a pressure midway between the systolic and diastolic values for 5 min. A positive result was recorded as ≥ 20 petechiae/in² read on the inner aspect of the forearm. Patients were palpated daily for liver enlargement, and hepatomegaly was recorded if the edge was ≥ 2 cm below the right costal margin. Blood samples were drawn by venipuncture on the day of admission or as soon thereafter as practical and on the day of discharge, and attempts were made to collect finger-prick blood samples daily in the hospital. All patients were asked to return 7–14 days after discharge for a convalescent blood sample.

Hematology

A complete blood cell count and hematocrit (Hct) determination were done on the admission and convalescent samples. The Hct and platelet count also were done on the daily finger-prick samples. Platelet counts were done by the hemacytometer method, and any count of $\leq 100,000/\text{mm}^3$ was classified as thrombocytopenia. An increase in the Hct of $\geq 20\%$ between daily readings taken while the patient was in the hospital or a decrease of $\geq 20\%$ in the convalescent Hct value compared to a reading taken while the patient was in the hospital was classified as hemoconcentration.

Virology and serology

The initial, day of discharge, and convalescent blood samples were tested for antibodies to all four DEN virus serotypes in a microtechnique hemagglutination-inhibition (HI) test.^{4,5} All sera from the same patient were tested simultaneously before final classification of antibody response. A fourfold or greater difference in HI antibody titer between the initial and any subsequent sample from the same patient against any of the DEN serotypes was considered diagnostic. All patients who seroconverted and had a HI titer of $\geq 1:1,280$ were classified as secondary (2°) DEN in-

fections, but if the HI titer in the convalescent sample taken 1–4 weeks after the onset of illness did not exceed 1:640, the patients were classified as primary (1°) DEN infections. Patients that did not seroconvert were considered presumptive recent secondary (2°) cases if the HI antibody titer for any serum sample was $\geq 1:1,280$ against any DEN serotype. The cut-off HI antibody titers for classifying 1° or 2° infections were based on background titers in 3,000 healthy school children from the area of Manila around SLH surveyed about one year after the 1983 epidemic. Less than 1% of these children had an HI titer $\geq 1:320$ against any of the DEN serotypes (C. G. Hayes, personal communication).

The initial blood sample from each patient also was assayed for virus. Two 25 cm² flasks containing confluent monolayers of *Aedes pseudoscutellaris* (LSTM-AP-61) cells were each inoculated with 0.02 cc of undiluted plasma from each patient. The cells were incubated at 28–30°C in Mitsuhashi-Maramorosch/Varma-Pudney (MM/VP12) medium containing fetal calf serum and antibiotics.⁶ Supernatant fluid from each flask in which the cells did not develop an obvious syncytial cytopathic effect (CPE) was passaged to fresh LSTM-AP-61 cells after 1 week. Cells from these second passage flasks were harvested after 7 days and fixed on teflon coated spot slides. If the cells in any of the first and second passage flasks developed CPE at any time during the incubation, spot slides were prepared immediately.

The cells fixed on the spot slides were examined for the presence of DEN viruses using a standard indirect fluorescent antibody technique. Cells from flasks in which the monolayer had not developed CPE were initially tested with a flavivirus group reactive monoclonal antibody (4G2). Cells that stained positive in this initial test and cells from all cultures with CPE were reacted with type-specific monoclonals to identify the serotype of DEN virus. The specific monoclonals, produced by hybridomas originally developed at the Walter Reed Army Institute of Research, were 15F3 (DEN-1), 3H5 (DEN-2), 5D4 (DEN-3), and 1H10 (DEN-4).^{7,8}

Classification of disease severity

The patients were classified clinically as DHF according to the criteria published by the World Health Organization (WHO).⁹ All confirmed cases not meeting these specific criteria were classified

TABLE 1

Classification of laboratory diagnosis in 517 dengue patients by the type of HI antibody response or by virus isolation

Laboratory diagnosis	No. of cases	%
Antibody response		
Seroconversion, 1°	30	5.8
Seroconversion, 2°	166	32.1
Seroconversion, unclassified	19	3.7
Presumptive recent, 2°	237	45.8
Virus isolation	65*	12.6
	517	100

* This number includes only those patients from whom virus was isolated and who could not be classified serologically.

as dengue fever (DF) with or without hemorrhagic manifestations.

Statistical methods

Geometric mean titers were compared using Student's *t*-test. All other comparisons were done using χ^2 with Yate's correction.

RESULTS

Epidemiologic findings

During the study period, 1,055 clinically diagnosed cases of hemorrhagic fever were admitted to SLH. Laboratory studies confirmed DEN virus infections in 517 (49%) of these patients (Table 1). Of the laboratory confirmed cases, 91% were residents of Manila, and the remainder came from other areas of Luzon Island where Manila is located. The number of cases increased steadily from May until the November peak with 69% of the infections occurring from October through December (Fig. 1). The age range of the confirmed patients was from <1 year to 47 years, and 78% of the patients were <15 years old (Table 2). The median age of the male and female patients was 9.9 years and 9.6 years, respectively, and the male to female ratio was 1:1.14.

Clinical and laboratory findings

Fever was the most common nonspecific presenting sign in the patients (Table 3). Although 100 patients were afebrile on the day of admission, only 7 of these gave a negative history of fever. Some type of hemorrhagic manifestation was recorded in 89% of the patients while in the

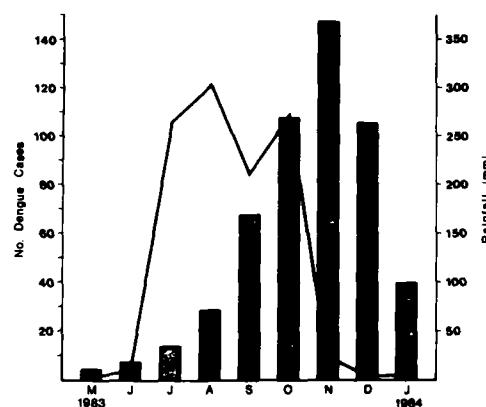


FIGURE 1. Number of confirmed dengue cases (■) at San Lazaro Hospital and monthly rainfall (—) in Manila from May 1983–January 1984.

hospital (Table 4), and this also was the major clinical finding prompting hospitalization. Shock was recorded in only 2 patients. Both of these patients, a 3-year-old male and a 3-year-old female, had a 2° type of antibody response, but no isolates were obtained. There were no fatalities among the confirmed patients. The most common hematological findings in the 517 confirmed cases were thrombocytopenia (71.8%), relative lymphocytosis (47.6%), and hemoconcentration (39.5%).

Combining the clinical and hematological findings, 110 (21%) of the confirmed cases could be classified as DHF: 5 grade I, 103 grade II, and 2 grade III. Of the remaining cases, 355 (69%) were classified as DF with hemorrhage, and only 52 (10%) were classified as DF without hemorrhage. A positive tourniquet test was the only bleeding manifestation that occurred at a significantly greater frequency in DHF patients than

TABLE 2

Age and sex distribution of confirmed dengue patients at San Lazaro Hospital, May 1983–January 1984

Age (years)	Male	Female	Total
0–4*	33	46	79
5–9	89	99	188
10–14	68	66	134
15–19	33	41	74
20–24	13	15	28
25+	3	7	10
Unknown	3	1	4
Total	242	275	517

* Only 3 patients were <1 year old.

TABLE 3

Nonspecific signs and symptoms recorded for 517 confirmed dengue patients on day-of-admission at San Lazaro Hospital, May 1983-January 1984

Finding	No. of cases	%
Fever	417	80.7
Malaise	247	47.8
Anorexia	221	42.7
Abdominal pain	219	42.4
Vomiting	170	32.9
Myalgia	164	31.7
Nausea	156	30.2
Cough	107	20.7
Sore throat	104	20.1
Hepatomegaly*	70	13.5
Injected pharynx	68	13.2
Arthralgia	62	12.0
Lymphadenopathy	55	10.6
Conjunctival injection	53	10.3
Chills	50	9.7
Rhinitis	36	7.0
Constipation	35	6.8
Eye pain	22	4.3
Diarrhea	16	3.1
Dyspnea	12	2.3

* ≥ 2 cm below the right costal margin.

in DF patients ($P < 0.05$). Epistaxis, on the other hand, was recorded more often in DF compared to DHF patients ($P < 0.01$). There was no significant difference in the type of HI antibody response of patients classified as DF or DHF; however, there was an association with the serotype of virus isolated. DEN-2 was recorded at a significantly higher rate from DHF patients (15.5%) than from DF patients (8.8%). DEN-2 also was the only serotype isolated more frequently from patients with evidence of gastrointestinal bleeding (melena or hematemesis) (16.9%) than from patients without gastrointestinal bleeding (9.3%); although the difference was not significant ($0.05 < P < 0.10$).

Virus isolation

DEN-2 virus was the only serotype with more isolates from sera with a homologous HI antibody titer $> 1:20$ (56.6%) than from sera with a homologous HI titer $\leq 1:20$ (43.4%), and the geometric mean homologous HI antibody titer (GMT) of sera from which DEN-2 was isolated was significantly greater than the GMT of sera from which DEN-1 or DEN-3 were isolated (Table 5). DEN-4 was not included in the comparison because of the small number of isolates. Most of the DEN-1 isolates were from sera with

TABLE 4

Hemorrhagic manifestations recorded on 517 confirmed dengue patients during confinement at San Lazaro Hospital, May 1983-January 1984

Finding	No. of cases	%
Positive tourniquet test	360	69.6
Petechiae	331	64.0
Epistaxis	230	44.5
Melena	49	9.5
Hematemesis	36	7.0
Gum bleeding	35	7.0
Ecchymosis	13	2.5
Hemoptysis	7	1.4

a homologous HI titer $< 1:10$ which corresponds with the significantly higher isolation rate of this serotype from patients classified by seroconversion as 1° cases (30%) compared to 2° cases (7.8%). The difference in isolation rates for the other 3 serotypes did not differ significantly between patients classified by seroconversion as 1° or 2° infections.

DISCUSSION

Based on the admission records at SLH for clinically diagnosed cases of hemorrhagic fever, the 1983 epidemic was the largest since 1972 in Manila. One factor that may have contributed to the development of this epidemic was the weather. The usual onset of the rainy season was delayed by about two months in 1983. The resulting water shortage may have resulted in more

TABLE 5

Distribution of 148 dengue virus isolates by serotype in relation to the homologous HI antibody titer in the acute serum of the patient from whom the virus was isolated

Homologous HI titer	Number of isolations			
	DEN-1	DEN-2	DEN-3	DEN-4
$< 1:10$	30	3	15	1
1:10	10	14	7	3
1:20	3	6	4	1
1:40	1	9	4	2
1:80	2	8	4	1
1:160	0	3	2	0
1:320	0	6	0	0
1:640	1	3	2	0
1:1,280	1	1	1	0
Total	48	53	39	8
*GMT	3.4 ^a	39.5 ^b	10.2 ^c	15.0

* GMT = geometric mean titer. Means followed by different letters were significantly different (t -test, $P < 0.05$). DEN-4 was not included in the analysis because of the small number of isolates.

long-term indoor storage of water than usual providing expanded breeding sites for *Aedes aegypti*. Drought conditions also were noted in Manila prior to the 1966 DEN epidemic.¹⁰ The delay in the start of the rainy season from mid-May to mid-July and a corresponding extension of the end of the rainy season from October to December probably accounted for the peak number of DEN cases occurring in November. During past epidemics, the peak number of cases usually has been reported in August to September with the epidemic terminating by October or November.^{3, 10}

The age and sex distribution of cases seen in the 1983 epidemic is similar to what was reported for confirmed cases in the 1966 epidemic except that there was a slight majority of male cases in the earlier outbreak.³ The bimodal age distribution of DEN cases reported from Thailand with the peak of primary infections occurring in infants has not been reported in the Philippines.¹¹

The lack of fatal outcome among patients at SLH with confirmed DEN infections in 1983 agrees with the studies conducted in 1966 when no deaths were recorded among 321 confirmed cases at two hospitals in Manila.^{3, 12} In the earliest outbreaks of hemorrhagic fever recorded in Manila a substantial number of fatalities were reported.¹³ Unfortunately, the diagnosis of these cases was not supported by virus isolation or serological tests.

The lack of fatal outcome in our patients is probably attributable to the absence of severe shock. Shock either preceding or following gastrointestinal bleeding has been identified as the major cause of death among hospitalized DEN patients in Thailand and Indonesia.^{14, 15} In these areas >30% of the hospitalized patients with DHF have been diagnosed as having dengue shock syndrome (DSS).^{16, 17} Among our 1983 DHF cases, shock was recorded in <2%, which is even lower than the 6.8% recorded for confirmed DEN patients at SLH during the 1966 epidemic.³ We only classified a patient as DSS if a narrowing pulse pressure or hypotension were recorded in the presence of clinical manifestations of shock such as cold, clammy skin, cyanosis, and restlessness. Many of our patients classified as DF with hemorrhage or DHF grades I and II had a narrow pulse pressure reading of ≤ 20 mm Hg at some point during their hospitalization without any other accompanying physical signs of shock.

The criteria used for classifying shock in the 1966 study were based on WHO recommendations published at that time, which were the presence of cool and blotchy skin, a rapidly narrowing pulse pressure, and then the development of imperceptible blood pressure and pulse (similar to the current grade IV classification).¹⁸ None of our patients developed undetectable blood pressure or pulse.

Hematemesis and melena also were reported more frequently in the 1966 outbreak (32.2% and 25%, respectively) than during the current study (Table 4); however, hepatomegaly was more common in 1983 compared to 1966 (1%).³ Hepatomegaly has never been reported as a frequent manifestation in hospitalized DEN patients in Manila. In fact, this was one of the clinical findings noted to differ between the first reported outbreaks of DHF described in Manila and Bangkok.² In Bangkok, 90% of hospitalized children with DHF have been reported to have enlarged livers.⁹

This is the first DEN epidemic in Manila in which the most frequently isolated serotype was DEN-2. In both the 1956 and 1966 outbreaks, DEN-3 predominated,^{1, 3} and in a 1964 study,¹⁹ DEN-4 was most commonly isolated from patients. The distribution of DEN serotypes also was different in the present compared to earlier outbreaks in that all four serotypes were isolated from hospitalized patients, and the number of isolates for three of the serotypes was not substantially different (Table 5). Although previously two or three serotypes have been isolated during an epidemic, a single serotype has always strongly predominated. These differences may be a reflection of the greater sensitivity of the mosquito cell culture isolation system used in this study compared to the newborn mouse and vertebrate cell culture systems used in the earlier studies.²⁰

The reason that most DEN-2 isolates were from sera with higher homologous HI titers compared to the other DEN serotypes is not clear, but conceivably could be related to an immune enhancement phenomenon. In experimental studies, monkeys challenged with DEN-2 virus following an earlier infection with a heterologous serotype had higher peak viremia titers than monkeys experiencing a 1° infection with DEN-2.²¹ This enhancement of peak titers was not seen with the other DEN serotypes in the monkey 2° infection model. Studies in Indonesia also have shown that

the geometric mean virus titers of patients experiencing a 2° DEN-2 infection were equivalent to titers in patients experiencing a 1° DEN-2 infection; whereas in patients experiencing a 2° DEN-1 or DEN-3 infection the geometric mean virus titers were about fivefold lower than in 1° infections with the same serotype.²² Our data is insufficient to confirm whether or not a similar situation was occurring in patients from whom DEN-2 was isolated in this study because we did not titer the virus isolates and the type of serological response was unknown in many of the cases.

In Thailand, DHF has been associated with 2° infections, and DSS in particular has been associated with 2° infections caused by DEN-2 virus.^{23, 24} In Indonesia, DEN-3 virus has been isolated most frequently from fatal cases.¹⁵ Within the more limited range of clinical severity seen in our patients, no significant association with any serotype was found; although, DEN-2 was isolated more frequently from patients with gastrointestinal bleeding than the other three serotypes. DEN-2 was significantly associated with DHF, but our DHF patients did not particularly differ in disease presentation from most of the DF patients except for the presence of concurrent thrombocytopenia and hemoconcentration in the former group. There also was no statistical association of 2° infection with DHF compared to DF in our study based on the HI antibody response pattern in patients who seroconverted. However, the fact that most of the hospitalized patients apparently were experiencing a 2° infection (Table 1) could indicate that 2° infections do cause more severe disease than 1° infections in this population regardless of whether or not they are classified as DF or DHF.

Overall our serological data is biased towards the diagnosis of 2° cases because of the combination of a low rate of return of patients for convalescent samples (about 32%) and the diagnosis of many 2° infections as presumptive recent cases based on a single or stable high HI antibody titer on samples taken in the hospital. Primary cases require properly paired sera to make a serological diagnosis using the HI test. However, the 2° to 1° case ratio was still 5.5:1.0 when only patients that had properly paired samples were included in the analysis. That the disparity between 2° and 1° infections seen in the hospital may be the result of more severe disease associated with 2° infections is further supported

by data on HI antibody rates in schoolchildren in the area of Manila around SLH where most of our patients lived. Only 29% of over 3,000 children from 6–10 years old were positive for DEN antibody (C. G. Hayes, personal communication). This suggests that 1° and 2° infections may not have resulted in equal rates of hospitalization in this population, and that the paucity of hospitalized patients experiencing 1° infections is not attributable to a lack of people without DEN antibody in this age group.

Some of the 538 undiagnosed patients in this study may have had DEN infections that were not confirmed because of their failure to return for a convalescent sample. This would be particularly true in the case of 1° infections as discussed above. However, since the 1983 epidemic a series of over 500 patients admitted to SLH with a clinical diagnosis of hemorrhagic fever has been studied and the proportion of unconfirmed cases, 52%, has remained similar (C. G. Hayes, personal communication). In this latter group, 75% of the patients had a convalescent sample drawn, and all sera was tested for anti-DEN IgM antibody using an antibody capture ELISA to increase the sensitivity of detecting 1° infections. These results indicate that a large number of patients with clinically suspect DEN infections actually do not have DEN. This may be related to the criteria used to select patients for admission to the DEN ward, which consist mainly of the presence of fever with acute onset accompanied by any bleeding manifestation. Serological studies with stored sera currently are in progress to diagnose other causes of hemorrhagic fever in these patients.

This study shows that DEN infections remain a common cause of pediatric hospitalization in Manila, and that disease resulting in hospitalization is apparently more commonly associated with 2° infection. The lack of cases with shock or massive hemorrhaging seems to contrast with the disease picture seen in other DEN-endemic areas of Southeast Asia, particularly Jakarta and Bangkok, where extensive studies have been conducted. The reasons for this difference remain to be defined.

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FIELD	GROUP	SUB-GROUP	dengue		
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19. ABSTRACT (Continue on reverse if necessary and identify by block number) From May 1983 to January 1984, 517 patients with laboratory confirmed dengue were studied at a hospital in Manila. Secondary dengue infections were diagnosed in 78% of these cases. Peak admission (28%) occurred towards the end of the rainy season in November. Most patients (78%) were 15 years old but only 3 were infants. Although some type of hemorrhagic finding occurred in 460 cases (89%), only 110 were classified as dengue hemorrhagic fever and the remainder as dengue fever with hemorrhagic manifestations. The clinical course was usually mild. Gastrointestinal bleeding was present in 65 cases, but only 2 patients developed shock. No fatalities occurred. → over → Dengue 2 was the predominant serotype with 53 isolates, followed by dengue 1 with 48 isolates, dengue 3 with 39 isolates, and dengue 4 with only 8 isolates. Dengue 2 was the only serotype with more isolates from sera with a homologous HI antibody titer 1:20 (57%) than from sera with a homologous HI titer 1:20 (43%). In					
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contrast, most of the dengue 1 isolates (63%) were from sera with a homologous HI antibody titer 1:10, and this serotype was strongly associated with primary infections.

→ This study shows that dengue infections remain an important cause of pediatric hospitalization in the Philippines; however, the occurrence of life-threatening dengue hemorrhagic fever as has been described in several other large urban areas of Southeast Asia appears to be rare. Reprints; (KT) —

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