WHY DENGUE HEMORRHAGIC FEVER IN CUBA?
I. SECONDARY INFECTION AS A RISK FACTOR FOR DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME (DHF/DSS).

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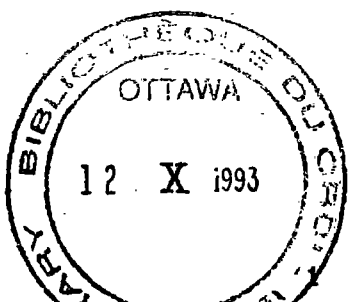
ABSTRACT

The role of sequential infection as a risk factor for the development of Hemorrhagic Dengue is discused considering the data obtained during the epidemic of DHF/DSS that occured in Cuba in 1981.

The results of the study of 3 groups of patients, with DHF/DSS, are presented. The percentage of secondary infection in these was between 95 and 98,5%. It is concluded that secondary infection is a necessary prequisite but other factors are necessary for the development of the disease.

INTRODUCTION

In 1954 (Hammond et al, 1957), an epidemic of "an apparently new disease" was reported in the Philippines.



This disease involved mainly children in whom a febrile clinical picture with numerous hemorrhagic manifestations was produced. Shock did not necessarily accompany the disease.

Hammon et al (1957) stated in 1957 that Dengue virus was the etiological agent of the disease .

Halstead (1965), analysed different epidemics that occurred during the XIX and XX centuries. This retrospective analysis showed that Dengue Hemorrhagic Fever (DHF), far from being a new disease, had already been observed during the epidemics in Australia (1827), Southern - United States (1922), South Africa (1927), and Greece (1928) (Ehrenkranz et al, 1971; Papaevangelov et Halstead, 1977; Schlesinger, 1977).

However, DHF/DSS acquired an epidemic character after the 1950's although it was limited to the South East Asia and the Western Pacific Islands regions, where it became one of the leading causes of infantile morbidity and mortality (Halstead,1980).

The etiopathogenesis of the disease has been widely discussed. Two main hypothesis have been proposed to explain the development of the severe clinical picture

of the disease. The first suggests that the viral virulence may vary in the different strains of the 4 Dengue virus serotypes and that DHF/DSS cases may be exceptions of Dengue infection (Rosen,1977).

Rosen (1977) considers that DHF/DSS appearance in South East Asia after 1953, is related with the increase of urban populations, the high density of the mosquito vector and the permanent circulation of the four serotypes of Dengue virus. All these factors, increased after World War II, would produce a rise in infection rates by dengue virus, thus favouring the appearance of severe cases.

It has been suggested that repeated passage of the virus between jungle monkeys and the Aedes albopictus mosquitoes leads to the selection of diferent strains of dengue viruses which might have a significant variation in their pathogenicity to man and which may be potentially hemorrhagic (Hammond, 1973).

Hammond (1973) stated the possibility of double infection of mosquitoes with 2 dengue virus serotypes leading to recombination or phenotypic mixture giving rise to more virulent viral strains.

The second hypothesis was proposed by Halstead (1970, 1981), who stated that the double dengue infection, or sequential infection, explains the etiopathogenesis of the disease. This hypothesis is based on the fact that DHF/DSS occurs in persons with antibodies (actively or passively acquired) to a dengue serotype, which in presence of a second infective serotype are capable of forming infectious virus-antibodies immunecomplexes.

It has been established that non-neutralizing concentrations of dengue antibodies are capable of forming immune complexes which attach to the monocyte by Fc receptor, activating phagocytosis and facilitating the entrance and replication of the virus into the cell. Since products from activated monocytes are capable of interacting with the complement and coagulation systems, and these cells generate a vascular permeability factor, then DHF/DSS can be related to the above mentioned phenomena (Halstead, 1979, 1982).

Prospective studies in Bangkok in 1962-1964 (Nimmannitya et al. 1969; Halstead et al, 1969 a,b,c,d,) and Ko Samui in 1966-67 (Winter et al, 1968) provided the first epidemiological data for such a hypothesis. The first study of DHF/DSS attack rates showed 1,8 cases of DHF and 0.07 cases of DSS in 1000 primary infection cases

and 20.1 cases of DHF and 11,4 of DSS per 1000 secondary infection cases.

Nevertheless, there have been scarce reports of DHF/DSS outbreaks, in which secondary infection was not documented. (e.g. the outbreak in Niue Isle in 1972) (Barnes et Rosen, 1974). During this outbreak, produced by dengue 2 virus, there were reports of cases with hemorrhagic manifestations and shock, including some fatal cases.

During the 25 years prior to this outbreak, no dengue virus was reported in the island and consequently the deaths with secondary infection were unlikely.

In spite of the wide circulation of dengue virus types 1, 2 and 3 in the Caribbean region, DHF/DSS was not known in the area, though there were reports of isolated cases with hemorrhagic manifestations in Puerto Rico and Jamaica (López-Correa et al, 1978; Fraser et al, 1978).

An epidemic of Dengue 1 ocurred in Cuba (Más, 1979) in 1977. It was characterized by a mild clinical picture, and over 400 000 persons were affected. It appeared after more than 30 years without apparent viral circulation.

In 1981, an epidemic of DHF/DSS caused by dengue 2 virus occurred in the country affecting over 300 000 persons; causing 10 000 reports of severe cases and 158 deaths (Kouri et al, 1983). The epidemic was eradicated by the 10th of October of that same year, after an intensive vector control campaing which is still mantained.

The epidemiological situation in the country is unique since a population almost totality susceptible to dengue virus has suffered 2 large epidemics by dengue virus types 1 and 2 in 4 years. The second epidemic was characterized by the hemorrhagic and shock clinical pictures.

The vector control campaign and the very low mosquito index makes unlikely circulation of dengue viruses at present. In this context retrospective seroepidemiological studies can be extremely valuable to determine such factors as the percentage of primary and secondary infections, the frequency of DHF/DSS attack rates per type of infection, the DHF cases frequency per each case of classical or subclinical dengue, etc.

MATERIALS AND METHODS

The objective of the present study was to determine if sequential infection by the two dengue serotypes was a

risk factor for the development of the severe clinical picture. To this end we studied the frequency of haemagglutination inhibition (HI) and neutralizing (NT) antibodies to dengue virus types 1 and 2 in three groups of patients clinically diagnosed as DHF/DSS cases.

RESULTS AND DISCUSSION

The first group (Guzmán et al, 1984) was composed of 103 patients (children and adults) admitted to hospital with a clinical diagnosis of DHF, grades II and III, (according to the Technical Advisory Committee for DHF/DSS) (World Health Organization, 1980), which was serologically confirmed by the study of paired sera, using the haemagglutination inhibition technique . Of these patients, 5 (5%) were primary infections and 98 (95%) were secondary infections (Table I). In this group, 91% of these cases of secondary infection had some hemorrhagic manifestation; 20 patients presented shock and among these only one suffered a primary infection .

The second group consisted of 124 children under 14 years of age admitted to hospital with DSS (grades III and IV), and the third of 104 adult patients, with DHF (grades II and III); neutralizing antibodies were determined, in all these patients.

As demonstrated in Table I only 2 (2%) children with DSS were primary infections and 122 were secondary infections. 2 out of the 104 adult patients were primary infections and 102 (98%) secondary infections.

Woodall et al (1981) in an analysis of the inappearance of epidemics of DHF/DSS on the American region stated, as a possible explanation, the low virulence of circulating dengue strains or the inadequate serotype sequence or time span between both infections. They concluded that, should Halstead's hypothesis be true, an epidemic of Dengue 2 in a 5-years period might be a disaster for the region, considering that in Puerto Rico, alone over half a million children under age 15 were immune to Dengue virus type 1.

This epidemiological situation was present in Cuba, in which 44,46% of the urban population had HI antibodies to dengue virus in 1978 (Cantelar et al, 1981). This shows high circulation of dengue virus type 1 during the 1977 epidemic. Four years later, a second major epidemic by Dengue 2 occurred (this virus has frequently been associated to DHF/DSS outbreaks) (Halstead, 1970); so the disaster predicted by Woodall et al (1981), occurred in Cuba.

In a study in Thailand, Sangkawibha et al (1984) pointed out that the sequence Dengue 1-Dengue 2 was the most virulent. This was the sequence that occurred in Cuba.

Rosen (1982) stated that the 1981 epidemic of DHF in Cuba, offers a unique opportunity to solve the problem of the risk of sequential infection. He pointed out that "it should be relatively simple, even in retrospect, to compare the prevalence of primary and secondary antibody response in the surviving DSS patients, with what would have been expected on the basis of the proportion of the population previously known to have been infected with dengue type 1 in 1977".

Considering that in 1978, 44.46% of the urban population was immune to Dengue 1 (Cantelar et al, 1981) it should expected that in the studied groups no more than this percentage, were cases of secondary infection, if sequential infection were not a risk factor for DHF. In the three groups of seriously ill patients (both children and adults), the percentages of cases of secondary infection were between 95 and 98,5%, which are highly significant figures in relation to the percentage of possible cases of secondary infection expected in the population.

These data support the fact that sequential infection acts as a risk factor for the development of DHF/DSS.

In most of our patients, secondary infection explained the development of the hemorrhagic episode. Nevertheless, there was a limited number of patients who only had antibodies to Dengue virus type 2. Thus, it is likely that some other host-related factors may act as risk factors for the development of the disease. In this respect, it should be stressed that genetically controlled diseases such as Asthma, Diabetes mellitus and Sickle Cell Anemia were significantly more frequent in DHF/DSS fatal cases than in the rest of the population (Bravo et al in this journal).

It is interesting to note that no seriously ill or fatal cases were observed in children aged 1 and 2, not yet born during the Dengue 1 outbreak, in which it was very much unlikely to document a previous infection. In graph I and II, we show the age of a group of fatal cases and a group of children (from two big hospitals) who suffered DSS but did not die .We couldn't found a single case in the 1 and 2 year age group.

The absence of fatal and severe cases in the 1 and 2 year age group is an important epidemiological observation, so far not reported in other epidemics. It is an

extraordinarily valuable observation that supports - Halstead's hypothesis of secondary-type infection, which is the only one that allows us to explain the above-mentioned fact. It is precisely the 1 and 2 year age group which, having the possibility of getting infected during the 1981 epidemic, was not yet born during by the 1977 epidemic. Thus, the possibilities of secondary-type infection could be considered almost null.

Children less than 1 year of age, who evidently were not born in 1977, could, however, have maternal antibodies which played the role of primary-type infection.

The data reported in the literature, and our findings, indicate that sequential infection plays an important role in the development of DHF, acting as a risk factor. However while it is a necessary prerequisite, it is not the only factor necessary for the development of the disease, given the great number of persons who, having suffered a secondary infection, did not present the severe clinical picture. This implies that there should be some other host-related factors which determine whether an individual suffers or not DHF/DSS.

ACKNOWLEDGEMENTS

The study reported in this paper is part of a research program on Dengue Hemorrhagic Fever, developed by the Instituto de Medicina Tropical "Pedro Kourí", La Habana, Cuba, with financial support by the International Development Research Center (IDRC), Ottawa, Canada.

The authors are grateful for the help and advice of Prof. S.B. Halstead and Prof. M.G.R. Varma.

TABLE I: TYPE OF INFECTION IN THE 3 GROUPS STUDIED OF PATIENTS WITH DHF/DSS.

	GROUP I* (Patients with DHF/DSS)		GROUP II** (Children with DSS)		GROUP III** (Adults with DHF/DSS)	
	No.	%	No.	%	No.	%
Primary Infection	5	(5)	2	2	2	(2)
Secondary Infection	98	(95)	122	(98)	102	(98)
TOTAL=	103		124		104	

*Detection of hemagglutination inhibiting antibodies.

**Detection of neutralizing antibodies.

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WHY DENGUE HEMORRHAGIC FEVER IN CUBA?
II. INDIVIDUAL RISK FACTORS FOR DENGUE HEMORRHAGIC FEVER/DENGUE SHOCK SYNDROME (DHF/DSS).

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ABSTRACT

During the Dengue Hemorrhagic Fever, Dengue Shock Syndrome (DHF/DSS) epidemic that occurred in Cuba in the summertime of 1981, we could identifique some individual risk factors for the development of the severe clinical picture or for the fatal outcome of the disease.

Several chronic diseases such as Bronchial Asthma, Diabetes Mellitus and Sickle Cell Anemia were significantly present in the studied groups, as compared with the prevalence rates previously reported in the Cuban population.

The results presented here, also reveal a significant marked predilection for the white race in DHF/DSS patients when these figures are compared to the data of race structure of the Cuban population obtained from the 1981 National Population Census.

INTRODUCTION

During the Dengue Hemorrhagic Fever (DHF) epidemic that occurred in Cuba in 1981, certain conditions were identified which appeared to influence the severity of the clinical picture, or its further evolution. The retrospective studies conducted in patients, children and adults, in whom DHF/DSS was serologically confirmed in 1981, as well as the detailed analysis of the clinical charts of fatal cases, resulted in the identification of some individual risk factors, which so far are not well characterized. In our opinion the presence of these factors in an individual host may increase the posibilities of an individual to develop the severe clinical picture, or to determine its fatal outcome. In this paper we present the individual risk factors identified, well as the epidemiological basis supporting our report.

MATERIAL AND METHODS

In order to know the possible risk factors for DHF/DSS, we studied the clinical charts of 98 fatal cases (72 children and 26 adults) clinically and anatomopathologically diagnosed as DHF/DSS patients; 103 patients of DHF/DSS grades II and III as classified by WHO's Expert

Committee for the study of Dengue Hemorrhagic Fever; 75 children with DSS (grades III and IV) and 104 adults with DHF (grade II) who had a favourable evolution. In the last 3 groups, the diagnosis of the disease was serologically confirmed.

The Chi Square test with Yates' correction was used in all comparison tests.

RESULTS

The individual risk factors identified in our studies are as follows:

- Secondary character of the infection
- Chronic diseases
  - . Bronchial Asthma
  - . Diabetes Mellitus
  - . Sickle Cell Anemia
- White Race

SECONDARY CHARACTER OF THE INFECTION:

It was analysed in the previous paper (Guzmán et al,1985) in this same number of the Journal.

CHRONIC DISEASES AS RISK FACTORS

Chronic diseases have been generically pointed out as possible risk factors in Southeast Asia (Halstead,S.B.1979). In our studies, we have been able to identify Bronchial Asthma, Diabetes Mellitus and Sickle Cell Anemia as individual risk factors for the occurrence of the severe clinical picture of the disease.

Bronchial Asthma was frequently found as a personal and/or family antecedent in DHF/DSS cases. The disease had a markedly higher incidence rate both in children and adults, as compared to the prevalence rates in the Cuban population.(Table I).

The figures in infant and adult fatal cases are double the frequency rate reported in the Cuban population, according to the 1983 National Survey on Bronchial Asthma Prevalence Rate (Rodríguez de la Vega et al, 1983). Non-fatal adult cases of DHF developed a mild clinical disease, and no difference was seen between the percentage of Bronchial Asthma in this group and the one existing in the population. Asthma was also observed in non-fatal infant cases of DSS, at a rate double the percentage reported in the Cuban infant population. All these differences were statistically significant ($p<0.01$).

Diabetes Mellitus was frequently observed in DHF/DSS cases as a personal antecedent in adult patients. (Table II).

Four per cent (4%) of DHF/DSS adult fatal cases suffered from Diabetes Mellitus and 2% of adults who evolved satisfactorily. Since the prevalence rate is 1% for the population (Mateo de Acosta et al,1973), the observed frequency rate was double in those cases of favourable evolution, and fourfold in adult fatal cases.

No personal antecedents of Diabetes Mellitus was reported in DHF/DSS fatal or severe infant cases.

Sickle Cell Anemia was frequently observed in DHF/DSS cases.(Table III).

It can be seen that the percentage of infant and adult fatal cases with Sickle Cell Anemia are much higher than the prevalence rate in the Cuban population (Martínez AntuÑa,G. 1985). All these differences were statistically significant ($p<0,01$). No Sickle Cell Anemia cases were identified among children with DSS or adults that had a favourable clinical evolution.

RACE AS A RISK FACTOR

The high incidence rate of the severe disease in whites was a constant observation during the 1981 epidemic. This observation was confirmed in all research work conducted by our Institute in relation to the epidemic. (Guzmán, et al 1984).

Table IV shows the different figures found in our studies.

The percentage of white people in all the groups studied is near or higher than 80%. All differences in relation to the racial structure of the Cuban population according to the 1981 census were statistically significant ($p<0,05$), with the sole exception of adult fatal cases which is similar to that observed in the population.

DISCUSSION

Chronic diseases have been pointed out as possible risk factors for the development of DHF/DSS, but the findings of Bronchial Asthma, Diabetes Mellitus and Sickle Cell Anemia with a high frequency rate in severe or fatal cases of DHF/DSS have not been reported before.

The mechanism by which these diseases influence the severity of the clinical picture is, so far, unknown.

It had been said that "the more immunocompetent the individual, the more severe the shock syndrome" (Halstead, S.B., 1979). In asthmatic patients with their component of hyperreactivity and frequent cardio-pulmonary lesions, a disease like DHF/DSS, that has a known immunological basis, must express a more severe clinical picture.

In our studies, the incidence rate of Diabetes Mellitus in adults with disease was higher than in the Cuban population. This situation was not observed in children- which is logical, if we consider that this disease usually has its expression later in life. In Cuba, according to the census of diabetic children, a prevalence rate of only 0.14 per 1000 was confirmed (Díaz, et al 1983). This low prevalence rate should influence the non-identification of Diabetes Mellitus as a risk factor in childhood.

In studies conducted by our group, we obtained a history of diabetes in 24% of the families of child fatal cases. If we take into account the genetic character of this disease, we can analyze the figures of family

history found and consider that in this group there should be a certain number of children who in the future would probably have been confirmed as diabetic patients.

In adults, the frequency rate of diabetic patients both in cases of favourable evolution and in fatal cases was higher than that observed in the population, although the sample analyzed was not big. Also the mechanism by which this disease influences the severity of the clinical picture is, so far, unknown.

Sickle Cell Anemia was found to have a high frequency rate in severe cases of Dengue Hemorrhagic Fever. It is logical if we consider that this disease is characterized by its hemorrhagic manifestations and that the patients, weakened by their chronic disease, had a torpid evolution.

When analizing Sickle Cell Anemia patients who died of DHF/DSS, we observed that the disease had a shorter evolution than in the rest of the fatal cases. Fifty percent of Sickle Cell in which Anemia cases expired in less than 24 hours. Of the 8 Sickle Cell Anemia fatal cases, 5 (63%) presented a preponderance of hemorrhagic manifestations and 3 (37%) shock. It should be pointed

out that 4 of them presented a Sickle Cell trait. The clinical picture in these patients was characterized by a rapid fatal outcome after the sudden increase in the severity of the disease.

In fatal and severe cases of DHF/DSS, the prevalence rate of these diseases (genetically controlled) is - higher than that observed in the population. The chronic diseases mentioned above as risk factors support the criteria that some genetic factors might play a part in the development of the most severe clinical pictures of Dengue Hemorrhagic Fever. Other diseases are likely to act as risk factors in other countries.

In the groups studied, the white race presented a higher frequency rate of DHF/DSS ($p<0.05$), with the exception of adult fatal cases. This might be explained by the existence within this group of 4 Sickle Cell Anemia patients associated to the black race and which is an individual risk factor. If we take out these 4 patients, the percentages of white fatal cases (74%) is higher than the Cuban population and is similar to data from the other white groups (Table IV).

So far, we do not have an explanation for the high frequency rate of DHF/DSS in whites. More research is

needed to determine whether the high frequency rate of DHF/DSS in whites is due to the white race behaving as an individual risk factor or if it is because the black race has a certain degree of resistence to DHF/DSS.

It will be necessary to validate under any circumstances, the above-mentioned risk factors and to search for new individual risk factors, in other countries.

ACKNOWLEGEMENTS

The study reported in this paper is part of a research programme on Dengue Hemorrhagic Fever carried out by the "Pedro Kourí" Institute of Tropical Medicine, Havana, Cuba, with financial support from the International Development and Research Centre (IDRC), Ottawa, Canada.

The authors are gratefull for the help and advice of Professor M.G.R. Varma.

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TABLE I

PERSONAL ANTECEDENTS OF BRONCHIAL ASTHMA IN THE GROUPS STUDIED, AS COMPARED TO THE PREVALENCE RATE IN THE CUBAN POPULATION.

Group Studied	Sample***	Population
Children with DSS	19/76 (25)	11%
Children fatal cases	16/71 (23)*	11%
Adults with favourable evolution.	7/104 (7)	7%
Adult fatal cases	3/23 (13)**	7%

* In one case risk factor data was not available.

** In 3 cases risk factor data was not available.

*** Patients with risk factor/total of patients (% with risk factor).

TABLE II

PERSONAL ANTECEDENTS OF DIABETES MELLITUS IN THE GROUPS STUDIED, AS COMPARED TO THE PREVALENCE RATE IN THE CUBAN POPULATION.

Group Studied	Sample***	Population
Adults with favourable evolution	2/104 (2)	1%
Adult fatal cases	1/23 (4)*	1%

* In 3 cases risk factor data was not available.

** Patients with risk factor/total of patients. (% with risk factor).

TABLE III

PERSONAL ANTECEDENTS OF SICKLE CELL ANEMIA IN THE GROUPS STUDIED, AS COMPARED TO THE PREVALENCE RATE IN THE CUBAN POPULATION.

Group Studied	Sample***	Population
Children with DSS	0	0.08%
Children fatal cases	4/71 (6)*	0.08%
Adults favourable evolution	0	0.08%
Adult fatal cases	4/23 (17)**	0.08%

* In 1 case risk factor data was not available.

** In 3 cases risk factor data was not available.

*** Patients with risk factor/total of patients. (% with risk factor).

TABLE IV

DHF/DSS PERCENTAGES PER RACE, IN DIFFERENT GROUPS STUDIED, AS COMPARED TO RACIAL STRUCTURE OF CUBA'S POPULATION ACCORDING TO THE 1981 CENSUS.

RACE	GROUP STUDIED					
	DSS cases-studied during the epidemic (103)	Children fatal cases (72)	Adult fatal cases (26)	Children with DSS retrospective study (75)	DHF adult patients retrospective study (104)	Cuban population*
	(%)	(%)	(%)	(%)	(%)	(%)
White	78	86	65	86	81	66
Mulatto	18	11	12	7	13	21.9
Black	4	3	23**	7	6	12

* 0.1% Asians.

** 4 (15%) of the black adult fatal cases had Sickle Cell Anemia.

WHY DENGUE HEMORRHAGIC FEVER IN CUBA?
III. AN INTEGRAL ANALYSIS.

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ABSTRACT

The epidemiological factors present in Cuba in 1981, when the Dengue Hemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS) epidemic occurred, were really exceptional when compared to that of other countries in the region.

Epidemiological evidence is reported, which demonstrates that the virulence of the circulating strain is an important element to be taken into consideration when analyzing an epidemic.

The two current hypothesis to explain the occurrence of DHF/DSS epidemics are validated in a well defined epidemiological situation. The conclusion is reached that neither Halstead's hypothesis on secondary-type infection nor Rosen's hypothesis emphazising the role played by the virulence of the circulating strain can explain all cases. Both authors have made valid observations in different epidemiological conditions.

An integrated, multifactorial and unifying hypothesis is submitted, which may be useful in interpreting all situations. It is based, mainly, upon a deep analysis of literature and the Cuban experience.

INTRODUCTION

Up to now, the determining factors for the occurrence of DHF/DSS epidemics have been widely discussed. The role of the sequential infection, or the virulence of circulating viral strains, as the decisive factors for the appearance of the severe picture of the disease, are currently discussed, and two hypothesis have been stated. (Halstead, 1979, 1980, 1981; Rosen, 1977, 1982).

In 1981, Cuba suffered an extensive outbreak of Dengue Hemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS) by dengue virus type 2 (Kourí et al, 1982). It was characterized by a high morbidity rate and the occurrence of severe and fatal cases (Kourí et al, 1982a a, 1982b, (Guzmán et al, 1984).

This epidemic proved the possibility for DHF/DSS to appear in the Caribbean, and the concern of all countries of the region has increased,considering the possible repetition of our bitter experience.

A detailed analysis of the epidemiological conditions present in Cuba, at the moment of the epidemic, is useful and necessary. It is also important to explain the criteria on the different factors, which in our opinion, each country should consider to evaluate its own risk.

In our two previous papers, in this issue of the Transactions, we discussed the individual risk factors for the development of DHF/DSS, identified in the Cuban experience. In this paper, we go deeper into the explanation of the epidemiological and viral factors that were present in our country during the outbreak and we present an integral analysis of the interactions among these factors, needed for the ocurrence of an epidemic.

The Cuban epidemiological situation was exceptional when compared to that of the other countries in the region, due to the following aspects:

1. The Cuban population was almost totally free of antibodies to dengue viruses before 1977 (the year in which dengue virus type 1 was introduced) (Cantelar and Fernández, 1975; Más, 1979), while the population of most of the other countries of the region had suffered successive infections by dengue 2 and 3 for over 25 years (Anderson et al,

1956; Russell et al, 1966; Spence et al, 1969). This, undoubtedly, determined a certain degree of immunity in part of the Caribbean population.

2. There was a high density of Aedes aegypti mosquitoes in all urban areas of the island.

3. In Cuba, sequential infection by dengue 1 and 2 occurred over a 3-year-period (Más, 1979; Kourí et al, 1982) while in other Caribbean countries the time interval was 10 years between the introduction of dengue 2 and dengue 3 , and 13 years between the introduction of dengue 3 and dengue 1 (Anderson et al, 1956; Russell et al, 1966; Spence et al, 1969; Russell, 1979).

4. In our case, the sequence of infection was Dengue 1/Dengue 2. A relationship has been reported between the appearing of the DHF/DSS epidemics, and this sequence (Sangkawibha et al, 1984).

In other Caribbean countries, the sequence of introduction of the different dengue virus serotypes, (1953, Dengue 2; 1963-64, Dengue 3; 1977, Dengue 1; 1981, Dengue 4) has not favoured the occurrence of secondary infection with a sequence ending in Dengue 2 since dengue virus type 2 was the first

serotype introduced in those regions. Nevertheless, sporadic cases might have occurred. The time span between the introduction of Dengue 1 and 4 in the region was 4 years (Centers for Disease Control, 1981). Thus,it is likely that part of the Caribbean population may have secondary infection with the sequence Dengue 1/Dengue 4,in a short period of time. However, until now, no outbreak of DHF/DSS has been reported in the area in which such a sequence is involved.

5. During the 1981 epidemic, over 300 000 cases were reported with, 10 000 reports of severe cases and 158 fatal cases (Kouri et al, 1982). This data indicates that DHF/DSS appears with a certain frequency in relation to the total amount of cases reported in an epidemic. Therefore, the existance of a wide viral circulation with high attack rates and consequently a large number of ill persons, seems to be necessary for the disease to be expressed as an epidemic.

6. Viral virulence apparently increased as the agent was successively passed in the human host, and this gave rise to an increase in the case fatality rate by the end of the epidemic.

Considering that there was no recent antecedents of DHF/DSS either in Cuba or in the region, the case fatality rate was expected to be high at the outset, decreasing towards the end of the epidemic.

The expected beha viour was based on the measures taken in Cuba, such as early hospitalization and therapy, organization of expert groups to advise public health services throughout the country, and the experience acquired by our physicians in handling of patients.

GRAPH I

Graph I shows the actual behaviour of this index, which differs from the one expected. The case fatality rate increased, above all, during the month of August. To plot the curve, 3 moments of high morbidity (June,July and August) were taken. Extreme points in which low morbidity might distort the analysis, were excluded.

During the epidemic, the seriously ill cases were reported daily. With this information, it was possible to calculate an index that we named "SEVERITY", which is the rate of seriously ill cases in

relation to the total number of patients reported in the same period of time. The graph clearly shows that Severity also increased in July and even more in August.

On the other hand, in an analysis of the clinical charts of fatal cases, death was encountered in spite of the timely therapeutic measures taken to prevent or treat, according to the case, hemorrhages and/or shock. We are convinced that in DHF/DSS there are a group of patients in whom homoeostasis disorders are so quick and profound that saving them is practically impossible.

In Cuba, all conditions were created to offer the population an efficient, specialized medical care and to reduce to a minimun the effects of the epidemic. Thus, we can affirm that the case fatality rate analysed here (0.46 x 1000 patients) - refers to the "unsavable cases". This fact points towards an interpretation of the observed phenomenon as derived from the virus-host interaction.

An increased viral virulence has been described when a virus is successively passed in a competent host. This may explain our observations. Rosen

(1977, 1982) has reported that all strains of dengue virus have not the same virulence and bases his hypothesis on the pathogenesis of DHF/DSS, precisely on viral virulence. We think that our findings support the criteria that viral virulence is a factor to be considered when analysing DHF/DSS outbreaks.

The time interval between a first infective bite and the occurrence of a second case of dengue could be roughly estimated, considering both the intrinsic and extrinsic incubation periods, as between 15 and 20 days. If the first cases were reported at the end of May, then the viral strain may have had a second passage in humans during the month of June, which gave rise in July to an increase in the number of severe cases (Graph I). At this level of passage, the case fatality rate had not yet demonstrated an ostensible in Subsequent to the third passage in humans, the severity of the disease had a maximum peak and the case fatality rate increased rapidly.

These statements, based on an epidemiological observation, may be of great importance, and support the observations of other authors in relation to

the possible increase in virulence of the viruses continuously circulating for several years, in South East Asia (Sumarmo et al, 1983).

Not only should we analyze the epidemiological and viral factors that influence the occurrence of the DHF/DSS epidemic,but also the "individual risk factors" which may lead to the appearance of the severe clinical picture in man. In our case, the following individual risk factors were detected:

1. Pre-existance of antibodies to dengue (Guzmán et al 1986).

2. Age, high frequency in children (Kourí et al, 1982).

3. Sex, high frequency in female (adults) (Díaz et al, 1984).

4. Race, high frequency in whites (Bravo et al, 1986).

5. Chronic disease, high frequency in Asthmatic, Diabetic and Sickle Cell Anemia patients (Bravo et al, 1986).

In South East Asia and the Western Pacific Islands, where the disease is endemic, there may be some other "individual risk factors" present.

The Cuban, experience validates the two hypotheses in a very well defined epidemiological situation. That is why we consider that useful, and perhaps conclusive data and information, will be obtained from the analysis of our epidemic.

It is our opinion, that none of the two hypotheses, separately, can explain all situations or cases, al though both authors have stated in different epidemiological conditions real and valid principles for the interpretation of these epidemics.

We consider that for an outbreak to appear, there should be coincidence of several factors: epidemiological, individual and viral.

GRAPH II

Graph II shows the intersection between the subgroups of factors determining the occurrence of an epidemic. It is precisely the concurrence of factors of these three subgroups, which give rise to DHF/DSS outbreaks.

Some of the individual risk factors such as race, sex, age and chronic diseases, are predisposing factors which make the disease more frequent in a certain race, age group, etc. The pre-existance of antibodies is the main

individual risk factor; a "necessary prerequisite but not the only factor mediating the occurrence of the disease. It might be pointed out that individual risk factors are the ones that determine the appearance of the disease in a particular person, from a given population.

The occurrence, of these individual risk factors, in the presence of the epidemiological and viral factors, determine whether persons with a secondary type infection present the clinical picture. Great importance is given by us to the intensity of the host response on the basis that not all human beings respond in the same way and intensity to any stimulus, including the immunological ones.

The epidemiological and viral factors are, in our opinion, the determinants for the disease to occur in an epidemic fashion.

In the light of current knowledge this integral hypothesis allows an interpretation of all epidemiological situations. At the same time, it facilitates the evaluation of the risk of a given population or person, to suffer the disease.

It is of utmost importance to determine other possible individual risk factors present in endemic areas, as well as to gain in the knowledge and certainty of epidemiological and viral factors pointed out here.

ACKNOWLEDGMENTS

The study reported in this paper is part of a research program on Dengue Hemorrhagic Fever, developed by the Instituto de Medicina Tropical "Pedro Kourí", La Habana, Cuba, financially supported by the International Development Research Center (IDRC), Ottawa, Canada.

The authors are gratefull for the help and advice of Prof. M.G.R. Varma.

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