

BODY OF REPORT

SEATO Medic Study No. 12 Hereditary Factors in the Pathogenesis of THF

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Objectives: It is the purpose of this investigation to study the hypothesis that inherited host factors influence the course of dengue virus infection. To test this hypothesis it is proposed to study the incidence of known genetic markers in patients with severe dengue infection (THF) as compared with the incidence of such factors in a representative sample of the total population at risk. A statistically significant difference in the incidence of inherited factors in THF cases as compared with the "normal" population or persons acquiring a minor infection with dengue would suggest the existence of other genetically linked factors which might control the pathogenesis of dengue virus infection.

Description: Dengue hemorrhagic fever is a severe disease, predominantly involving children, caused by dengue viruses of several antigenic types. The disease is characterized by non-icteric hepatitis, cardiovascular collapse, thrombo-

cytopenia, various bleeding phenomena interstitial pneumonitis and serous effusions. Arthralgia and leukopenia are not common. The case fatality rate among patients receiving hospital care varies between five and ten per cent. The disease picture described is obviously at variance with that of classical dengue fever. This latter disease, which has occurred in large pandemics in the Caribbean and Mediterranean basins and in the Western Pacific, is characterized by fever, arthralgia and leukopenia but absence of mortality in children or adults.

In the course of seven years of observation in Bangkok it has been the consistent experience that only Asians acquire hemorrhagic fever while Europeans and Americans presumably exposed to dengue "hemorrhagic fever" viruses develop classical dengue fever. In general, in these latter ethnic groups, illness has been more severe in adults and somewhat milder in children. Dengue infections in Caucasians are associated occasionally with spontaneous petechiae, thrombocytopenia and positive tourniquet test (also noted in dengue outbreaks elsewhere in the world).

The appearance of two distinct disease entities caused by the same or related viruses had led to the hypothesis of the emergence of mutant "hemorrhagic" dengue strains. On the other hand, side by side occurrence of hemorrhagic fever and dengue fever in Asians and Caucasians in Bangkok has given rise to the alternate hypothesis that host factors influence the course of dengue infection. These factors might be acquired, such as immunologic or dietary status, or might be inherited. It is the purpose of this investigation to study this latter hypothesis.

To test this hypothesis comparison is made of the prevalence of human characters known to be genetically controlled in serologically proven dengue hemorrhagic fever with controls who have serologic evidence of dengue infection but no history of hemorrhagic fever. A statistically significant difference in the prevalence of inherited markers in the two groups could be interpreted as suggesting the existence of other genetically linked factors which might control the pathogenesis and course of dengue infection. Absence of detectable differences in the two groups, of course, would neither confirm nor deny the hypothesis.

Progress: Studied patients: Dengue hemorrhagic fever. Heparinized plasmas were obtained beginning in February 1964 from patients with clinical hemorrhagic fever hospitalized at the Children's Hospital and in July 1964 on the Thai Hemorrhagic Fever Study Ward. Acute and convalescent plasmas were tested by hemagglutination-inhibition (HI) tests using chikungunya and dengue type 1 antigen. Those patients with four-fold or greater titer rise or with fixed titers of 1:640 or higher in paired specimens were considered to have had recent dengue infection and were included in study.

Controls. Plasmas were collected from well children, surgical patients with miscellaneous febrile illnesses seen at the Children's Hospital and several Maternal Child Health Centers in Bangkok. Patients with a past history of hemorrhagic fever were excluded. Serums were tested by HI against dengue 1

Table 1
 DISTRIBUTION OF BLOOD GROUPS, GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY AND
 HEMOGLOBIN TYPE IN THAI AND CHINESE CHILDREN WITH AND WITHOUT DENGUE HEMORRHAGIC FEVER.

HF status	Sex		Race				Blood Group				G-6-PD			Hgb Type		
	M	F	Th	Ch	A	B	O	AB	MN	M	N	N1	Def	A	AE	Other
Dengue	No. $\frac{91}{216}$	$\frac{125}{216}$	$\frac{178}{216}$	$\frac{38}{216}$	$\frac{61}{216}$	$\frac{66}{216}$	$\frac{73}{216}$	$\frac{16}{216}$	$\frac{112}{181}$	$\frac{43}{181}$	$\frac{26}{181}$	$\frac{197}{295}$	$\frac{8}{205}$	$\frac{172}{191}$	$\frac{16}{191}$	$\frac{1}{191}$
	% 42.12	57.87	82.40	17.59	28.24	30.55	33.79	7.40	61.87	23.75	14.36	96.09	3.90	90.05	8.37	1.57
Control 1 (Dengue infected but no HF)	No. $\frac{97}{177}$	$\frac{80}{177}$	$\frac{141}{177}$	$\frac{36}{177}$	$\frac{33}{177}$	$\frac{68}{177}$	$\frac{65}{177}$	$\frac{11}{177}$	$\frac{88}{159}$	$\frac{55}{159}$	$\frac{16}{159}$	$\frac{162}{171}$	$\frac{9}{171}$	$\frac{159}{170}$	$\frac{11}{170}$	
	% 54.80	45.19	79.66	20.33	18.64	38.41	36.72	6.21	55.34	34.59	10.06	94.73	5.26	93.52	6.47	
Control 2 (Total studied with no history of HF)	No. $\frac{178}{325}$	$\frac{147}{325}$	$\frac{250}{325}$	$\frac{75}{325}$	$\frac{64}{325}$	$\frac{122}{325}$	$\frac{120}{325}$	$\frac{19}{325}$	$\frac{177}{296}$	$\frac{93}{296}$	$\frac{26}{296}$	$\frac{301}{317}$	$\frac{16}{317}$	$\frac{281}{307}$	$\frac{26}{307}$	
	% 54.76	45.23	76.92	23.07	19.69	37.53	36.92	5.84	59.79	31.41	8.78	94.95	5.04	91.53	8.46	

and chikungunya antigens. Patients with dengue HI antibodies of 1:20 or higher were considered to have had at least one past dengue virus infection and were included in study.

Summarized in Table 1 is the distribution of blood groups, hemoglobin type and G-6-PD deficiency in patients with hospitalized dengue hemorrhagic fever and in controls. The age and race composition of the two compared groups were nearly equal. There were slightly more females in the HF group and more males in the control group. The distribution of AB, O and M and N groups is not identical in each group. Application of the chi square test to the distribution of blood types within each major blood group, however, shows that these variations could have occurred by chance (for the ABO groups vs control #1 $X^2(3) = 5.86$, vs control #2 $X^2(3) = 6.82$; for the MN group vs control #1 $X^2(2) = 5.63$ and vs control #2 $X^2(2) = 5.05$). No difference was observed in distribution of blood group, G-6-PD or Hgb type in hemorrhagic fever with or without shock (data not shown).

Conclusions: No evidence has been found which would support the hypothesis that patients acquiring hemorrhagic fever syndrome with dengue virus infection are genetically different from controls. Failure to find significant differences in blood groups in dengue hemorrhagic fever patients versus controls, unfortunately is not a significant test of the hypothesis.