LEADING ARTICLE

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DENGUE VIRUS INFECTION

While classical dengue (DF) has been known to exist in the tropical regions of Southeast Asia for more than two centuries, dengue haemorrhagic fever (DHF) was recognised as a new disease entity in 1953 when it appeared in the Philippines (1,2). In subsequent years both epidemic and endemic forms of DF/DHF were reported by several Asian and Southeast Asian countries including Thailand, Malaysia, Singapore, Indonesia, Vietnam, Lao People's Democratic Republic, Democratic Kampuchea, southern China, Burma and India, as well as by northern Australia, the South Sea Islands, the tropical areas of Africa and America and the Caribbean Islands (3). Haemorrhagic dengue has become established as one of the most important causes of morbidity and mortality among children in the Southeast Asian region (2).

DHF was first reported in Singapore in 1960 following which epidemics occurred annually from 1961-64 and 1966-68 (4,5). In 1969, a national *Aedes* control programme was instituted which resulted in reduction in the incidence of the disease. However, in 1973, the largest recorded epidemic, with 1187 reported cases, occurred, followed five years later by a smaller epidemic in 1978. Although vector control measures were reviewed and intensified, foci of infection continued to occur from 1979-85, culminating in another three epidemics in 1986, 1987 (5) and 1989.

The dengue virus, which causes both classical dengue and DHF, is a member of the family *Flaviviridae* to which also belongs the related yellow fever virus. There are four serotypes of the dengue virus with strain differences within each serotype. All four types cause both classical and haemorrhagic dengue, although a greater number of severe cases of DHF have been associated with infection by types 2 and 3 (3). Infection with each serotype is followed by the development of solid immunity to the homologous type, but only partial and temporary immunity to the heterologous types (2).

Dengue is transmitted by mosquito bite and man appears to be the main reservoir, although natural infection of monkeys does occur and may play a role in sylvatic transmission (3). *Aedes aegypti* is the most important vector, but in Singapore, *Aedes albopictus* is also a vector (6).

There are two views on the pathogenesis of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). One view is that the severity of the disease is related to the virulence of the infecting strain, and the other, that pre-existing antibody to a heterologous type (whether acquired by past infection or by transplacental transfer from the mother) induces enhanced infection. Subneutralizing levels of heterotypic antibody are believed to combine with the infecting strain and present the virus to mononuclear phagocytes by attaching to Fc receptors present on the cell surface. Intracellular replication of the virus then follows (7,8). In favour of the second "immune enhancement" hypothesis is the observation that DSS occurs at high frequency in children who have experienced previous dengue infection and in infants with waning, and therefore non-protective, levels of maternal antibody. Studies have shown that sequential infection ending with that by a type 2 virus (Thailand, Cuba) or a type 3 virus (Indonesia) have resulted in haemorrhagic dengue (2). Antibody-dependent enhancement has also been demonstrated *in vitro* by a number of laboratories for dengue and other flaviviruses (1,9).

Vector control, however efficient, will never eradicate the infection, as evidenced by the situation in Singapore. However, until an effective and safe vaccine becomes available, it remains the only means of control for this disease. Efficient surveillance is essential for effective vector control. At present in Singapore, 70-80% of notifications for DHF come from hospitalised cases. This automatically implies under-reporting, because for most infectious diseases, hospitalised cases constitute only the tip of the iceberg for the problem. Further, reports based on clinical and haematological findings alone are relatively inaccurate, as demonstrated in the accompanying paper by Pang et al who found that only about 40% of such cases could be confirmed by viral studies.

These authors have described a relatively simple method by which laboratory diagnosis can be made available to outpatients attending government and private clinics. This, by extending case sampling and improving the accuracy of diagnosis, would significantly improve surveillance for this important disease.

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