Cities spawn epidemic dengue viruses

Duane J Gubler

Major countrywide and regional epidemics of dengue and dengue hemorrhagic fever occur in Southeast Asia every three to five years. A model examining the spread of epidemic dengue in Thailand helps explain why such patterns occur.

Descriptions of illness clinically compatible with dengue fever date back almost 400 years[1]. In centuries past, epidemics or regional pandemics of dengue fever occurred every 10–40 years in tropical regions of the world. That pattern has shifted dramatically in the last century. Every three to five years, epidemics of dengue and its deadly cousin, dengue hemorrhagic fever (DHF), rage through countries in Southeast Asia. We now have an explanation for this epidemic pattern. In the 22 January issue of *Nature*, Cummings *et al.*[2] provide evidence for the emergence of new epidemic virus strains in Bangkok. These virus strains then spread outward into other locations in the country, causing epidemics.

In the past, the long intervals between epidemics were thought to result from infrequent introductions of new virus strains and serotypes, because of their dependence on ships for movement between regions[1]. After World War II, however, the frequency of epidemic dengue fever increased dramatically, with progressively larger epidemics and the emergence DHF, a severe and sometimes fatal form of the disease.

In the 1960s and 1970s, the epidemics were mainly confined to the major urban centers of Southeast Asian countries. In the past 25 years, however, the epidemics have spread to new geographic locations within those countries, with reports of many thousands of cases. In most countries of the region, the epidemics occur in cycles of three to five years, as illustrated in data from Thailand, Vietnam and Indonesia, countries that have had good long-term surveillance (**Fig. 1**)[3]. During this period, epidemic dengue fever and DHF have spread progressively throughout these countries.

Dengue fever and DHF are mosquito-borne diseases caused by four closely related viruses—DEN-1, DEN-2, DEN-3 and DEN-4 (ref. 4)—belonging to the family *Flaviviridae* and the genus *Flavivirus*. Infection by one serotype provides life-long immunity to that virus, but does not confer protection against the other three. Dengue viruses are the most important arboviruses causing human disease, with 2.5–3 billion people living in areas of risk, and an estimated 50–100 million new infections each year[3].

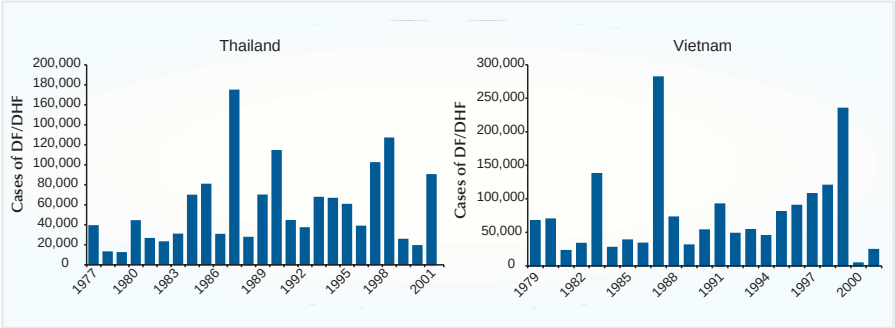

Figure 1 The dynamics of dengue. Thailand and Vietnam show epidemic patterns of dengue fever (DF) and DHF typical of tropical regions, with spikes about every three to five years. Cummings *et al.* now examine this pattern and point to cities as the prime breeding grounds for new epidemic virus strains, data from WHO.

Demographic and societal changes over the past 50 years have been responsible for the dramatic global spread of dengue viruses and the mosquitoes that transmit them. The result has been the cocirculation of multiple virus serotypes (hyperendemicity) in most large cities of the tropics, where the dengue viruses are maintained during interepidemic periods. Based on the emergence and spread of epidemic DEN-3 in Indonesia in the 1970s, it was speculated that new genetic variants of viruses, with greater epidemic potential and virulence (epidemic strains), emerge in this urban environment and then spread to new areas[5].

Cummings *et al.* provide the first good data to support this hypothesis. The authors use a new analytic technique—empirical mode decomposition—to demonstrate the existence of epidemic waves of dengue that originated in Bangkok and spread throughout Thailand every three years. Although the pattern of epidemic dengue in Thailand and other Southeast Asian countries every three to five years has been well documented, the origin of these epidemics has not. Cummings *et al.* show that each of the epidemics in Thailand, for the 15-year period from 1983 to 1997, originated in Bangkok and spread to the rest of the country (in waves traveling on average at 148 km/month). This observation supports the hypothesis that dengue viruses with greater epidemic potential originate in large urban centers of the tropics, and that these virus strains move throughout the country, causing epidemics in smaller communities[5].

What is not known is the genetic mechanism of virus changes, such as mutations or recombination, that allow the new epidemic strains to emerge; to understand that will require considerably more molecular epidemiologic research. The data presented by Cummings *et al.* are of great public health importance, however, because they tell officials in dengue-endemic countries that they should focus their limited prevention and control resources on the large cities of their country. If successful, this control strategy could prevent the emergence of new epidemic virus strains and, thus, the periodic epidemic waves that have become major public health problems in most Southeast Asian countries.

Effective prevention and control of dengue fever and DHF require good surveillance systems. Although calls have been made to improve surveillance for dengue fever and DHF in endemic countries for years[5–7], little progress has been made, primarily because most dengue-endemic countries do not have good virus diagnostic laboratories to support surveillance. Moreover, surveillance for the disease in the large urban centers that spawn the epidemic virus strains has deteriorated in the past 20 years because it is more difficult to work in urban

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areas. As the viruses spread within the countries, more emphasis has been placed on outlying areas where people are more cooperative.

Cummings *et al.* underscore the need to develop more effective laboratory-based surveillance for dengue fever and DHF in the large urban centers of the tropics. With modern technology, dengue viruses can be isolated, identified and genetically characterized in a short period of time. With more surveillance data and experience, it is likely that the genetic changes that give rise to dengue strains with greater epidemic potential and virulence will be identified, distinguishing them from the endemic strains that are maintained during interepidemic periods in specific urban centers. These kinds of studies should ultimately allow potential epidemic strains to be identified before they become widespread and cause epidemics throughout the country. Such an early-warning system is the first step to effective prevention and control of epidemic dengue fever and DHF, and to decreasing the public health and economic impact of this important tropical disease[7,8].

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Ceramide lances the lungs

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Ceramide may mediate several causes of acute lung injury and provide the basis for new therapeutic approaches for this severe, hard-to-treat condition (pages 155–160).

Acute lung injury, particularly its most severe form, acute respiratory distress syndrome (ARDS), is one of the most common reasons for admission to critical care units. Patients often die by drowning as a result of fluid leaking into the lungs from damaged capillaries. Acute lung injury can originate locally, for instance during severe pulmonary infection or acid inhalation, or systemically, after trauma or sepsis.

Many mediators have been implicated in acute lung injury, including tumor necrosis factor-α (TNF-α), platelet-activating factor (PAF) and prostaglandins. Yet blocking these individual mediators has not yet proven to be effective in clinical trials[1]. The disappointing results suggest that a single mediator does not predominate, or that several parallel and interacting mechanisms are involved.

In this issue, Göggel *et al.*[2] home in on a molecule that seems to integrate several inflammatory and injurious mechanisms. They find that the sphingolipid ceramide may be activated by PAF and other stimuli of acute lung leakage, resulting in pulmonary vascular leakage and edema.

Ceramide has long been recognized as a signaling molecule in the inflammatory response. It acts as a second messenger in the signal transduction pathway triggered by several agents of stress, including oxidative stress, acid and ionizing radiation, and extracellular stimuli such as proinflammatory cytokines and lipopolysaccharide[3]. Ceramide is generated from membrane sphingomyelin through the extracellular enzyme acid sphingomyelinase (ASM), which is secreted by cells such as endothelial cells and alveolar macrophages in response to inflammatory stimuli[4].

The stress response mediated by ceramide has been implicated in many diseases, including atherosclerosis, neurodegenerative diseases and AIDS. Ceramide activates the transcription factors nuclear factor-κB and

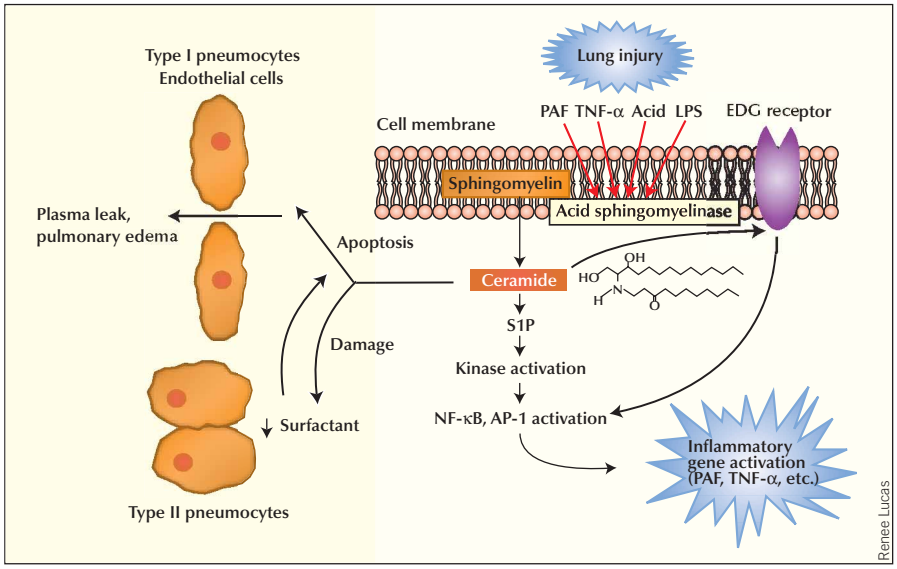

Figure 1 Generation of ceramide in endothelial cells. Ceramide is produced from membrane sphingomyelin by the enzyme acid sphingomyelinase, which is activated by several causes of lung injury, including platelet-activating factor (PAF) and tumor necrosis factor-α (TNF-α). Ceramide generates sphingosine-1-phosphate (S1P), which in turn activates the transcription factors (NF-κB) and AP-1. Secreted S1P can activate G-protein-coupled receptors, including endothelial differentiation gene (EDG) receptors. Ceramide may also induce endothelial cells to produce inflammatory mediators, such as PAF and TNF-α, thus perpetuating injury. Ceramide may also induce apoptosis of endothelial cells and type I pneumocytes, and damage TypeII pneumocytes, thus leading to pulmonary edema.

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