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Dengue: Overview and History

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Dengue fever is a benign syndrome caused by several arthropod-borne viruses and characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia and lymphadenopathy. Dengue hemorrhagic fever (DHF) is a severe, often fatal, febrile disease caused by dengue viruses characterized by abnormalities of hemostasis and capillary permeability that leads, in severe cases, to a protein-losing shock syndrome (dengue shock syndrome, DSS). It is thought to have an immunopathological basis. There are no synonyms for dengue viruses in current use in the English language. There is general agreement that there are four antigenically distinct members of the dengue subgroup of the genus *Flavivirus*.^{1,2} These are named dengue types 1 through 4. Historical synonyms for the dengue fever syndrome are bilious remitting fever, la dengue, dandy fever, breakbone fever and breakheart fever. Synonyms for DHF include infectious thrombocytopenic purpura, dengue shock syndrome, and Philippine, Thai or Singapore hemorrhagic fever.

Host Range

Inoculation of dengue strains of known human pathogenicity does not produce demonstrable infection in adult chickens, lizards, guinea pigs,

rabbits, hamsters or cotton rats.^{3,4} Many genera of subhuman primates are susceptible to infection by dengue viruses. Species belonging to *Macacus*, *Pongidae*, *Certhopicicus*, *Cercocebus*, *Papio*, *Hylobates* and *Pan* can be infected by bites of virus-infected mosquitoes or by injection of infectious virus preparations.^{4,5} Infection is essentially asymptomatic but viremia occurs at levels sufficient to infect mosquitoes. Simmons and colleagues⁵ were the first to note that wild-caught *Macaca philippinensis* resisted dengue infection, whereas *Macaca fuscatus* (Japanese macaque) were susceptible. Work in Malaysia has revealed an extensive jungle dengue transmission cycle involving canopy-feeding monkeys and *Aedes niveus*, a species that feeds on both monkeys and humans.⁶ In the early 1980's an extensive epizootic of dengue virus type 2 involving subhuman primates was recognized over a wide area of West Africa.⁷ During successive epizootics, dengue 2 strains have been recovered from humans after being transmitted by mosquitoes that also feed on subhuman primates.⁸ Sylvatic dengue 2 strains were poorly transmitted by the urban vectors *Aedes aegypti* and *Aedes albopictus*.⁹ By contrast, *Ae leutocephalus* and *Ae furcifer*, probable sylvatic vectors in Africa, readily transmitted urban dengue 2 viruses.¹⁰ As yet, urban dengue 2 viruses have not been isolated from infected subhuman primates in Africa. From genetic and epidemiological studies, it has been concluded that urban human dengue and jungle monkey dengue are relatively compartmentalized.¹¹ The full geographic range of the zoonotic cycle, the range of mosquito vectors and the composition of the subhuman primate zoonotic reservoir are not known.

In the urban cycle, dengue is vectored by anthropophilic mosquitoes that breed in and around human habitations. The virus travels along routes of transportation. Although there are important genetic differences between human and monkey dengue viruses and it is surmised that zoonotic viruses do not readily enter the urban cycle,^{11,12} the question whether dengue viruses can be reintroduced from the sylvatic cycle may become important if intensive vaccination should eradicate one or more types from a major region. If human herd immunity lessens and if populations of *Aedes aegypti* are left undisturbed, zoonotic dengue viruses might reseed into the urban cycle.

Geographical Distribution

Dengue fever outbreaks have been documented on every continent except Antarctica.¹³ During the 18th and 19th centuries, epidemics occurred in newly colonized lands, largely because of the necessity for domestic storage of water in frontier areas. Shipboard or garrison outbreaks often confined to nonindigenous settlers or visitors were reported in Africa, the Indian subcontinent and Southeast Asia.^{3,14–16} It is not known how many dengue viruses have been introduced into the Western Hemisphere since international commerce began after 1492. The American genotype of dengue 2, first isolated in Trinidad in 1951, may have been transmitted in the American tropics for much of the 20th century and is likely to have been the cause of the outbreaks in Panama and Cuba prior to World War II.^{17,18} During WWII, dengue virus infections were common among combatants in the Pacific, spreading to staging areas such as Japan, Hawaii and Polynesia.¹⁹ In the 50 years since WWII, following the introduction of all four serotypes from Southeast Asia, major outbreaks of DHF have occurred in the Pacific islands, tropical America and South Asia.^{13,16,20–22}

Dengue 1 of Asian origin appeared in the Caribbean in 1977, and spread to and remained endemic in coastal Central and South America, Brazil and Mexico.^{16,20,23} This virus briefly visited the United States along the Texas–Mexico border. A sharp outbreak of Southeast Asian genotype dengue 2 hospitalized 116,000 persons on Cuba in 1981 — the hemisphere's first DHF/DSS epidemic.²⁴ In 1986–90, dengue 1 spread throughout most of coastal Brazil, and from there to Paraguay and then to Peru and Ecuador.¹⁶ In 1990, more than 9000 dengue cases were reported from Venezuela; 2600 of them were classified as DHF, with 74 deaths reported. Dengue types 1, 2 and 4 viruses were isolated from this outbreak. Since then, DHF/DSS has spread to Colombia, French Guiana, Guyana, Brazil and Nicaragua, and to a smaller extent Puerto Rico. An interesting outbreak of American genotype DEN 2 resulted in thousands of secondary infections in Iquitos, Peru, but did not result in any DHF/DSS cases.²⁵ In 1995, dengue virus type 3 was introduced into the region.¹⁶

Dengue 1 and 2 viruses were recovered from humans with mild clinical illnesses in Nigeria in the absence of epidemic disease.²⁶ In 1983, dengue virus type 3 was recovered from Mozambique.¹⁶

DHF-like disease was described clinically in Thailand from 1950 and in the Philippines from 1953. DHF was first described in Singapore and Malaysia in 1962, Vietnam in 1963, India in 1963, Ceylon (Sri Lanka) in 1965, Indonesia in 1969, Burma in 1970, China in 1985, and Kampuchea and Laos from about 1985.^{16,27,28} Large outbreaks of DHF were reported from Sri Lanka and India since 1988, French Polynesia since 1990, Pakistan in 1992 and Bangladesh in 2000.^{16,29} These outbreaks of severe disease had been preceded by periods of silent dengue transmission.³⁰

Disease Burden and Cost

Disease burden

For more than 40 years, countries endemic for DHF have reported hospitalized cases and deaths to regional WHO offices. Samples from reported cases, in some instances, have been serologically verified. While there may be underreporting, it is unlikely to be of an order of magnitude. For the period 1956–2004, Table 1 lists the geographic distribution of 4,975,807 DHF cases (an unknown but small number are dengue fever) and 68,977 deaths (1.4% C.F) reported to national health authorities. Clearly, DHF is a huge problem in Southeast Asia. Note that the 67,295 deaths over a 40-year period in Asia means an average of 1682 per year. The highest number of DHF deaths reported to WHO has never exceeded 2500.

Dengue fever cases are reported most notably from the American hemisphere and the Pacific Islands, with 6.9 million case reports over the past four decades (Table 2). The numbers have escalated decade by decade.

Table 1. Dengue hemorrhagic fever cases and deaths reported to WHO regional offices, 1956–2004.

Western Pacific		Southeast Asia		Eastern Mediterranean		Americas	
C	D	C	D	C	D	C	D
2,822,263	35,632	2,028,058	31,663			125,486	1682

Table 2. Reports of dengue fever cases by region, 1960–2004.

Years	Americas*	Pacific Islands†
1960–1969	88,219	
1970–1979	774,797	
1980–1989	1,030,723	11,175
1990–1999	2,708,631	43,550
2000–2004	2,200,603	50,085
Total	6,802,973	104,810

*Reports to PAHO. †Reports to WPRO.

The reliability and completeness of reports of dengue fever cases have not been subjected to research scrutiny.

When encountered by susceptible individuals, strains of some serotypes may result in inapparent human infections. For example, when a Southeast Asian genotype dengue 2 virus circulated in Santiago de Cuba in 1997, over 95% of primary infections in adults were silent.³¹ But, in this same outbreak, virtually all adults who were immune to a different dengue serotype (dengue 1 in this instance) became ill when infected with dengue 2, with illnesses varying from classical dengue fever to DHF. Other types are more virulent. Virgin soil outbreaks of dengue 1 usually result in febrile disease, often with high attack rates.³² Simmons *et al.*,⁵ who infected susceptible adult volunteers, using mosquitoes serially transferred a single strain of dengue 1 and observed virtually 100% overt disease. In 1995, an American genotype dengue 2 was introduced into Iquitos, Peru. Only a small number of mild febrile illnesses were reported to health authorities, none with DHF.²⁵ It was surprising, then, to find that more than 80% of the population had been infected with dengue 2 while at the same time 60% experienced secondary dengue infections.

These studies are important, because despite the large number of cases of DHF and dengue fever reported throughout the world it can be anticipated that vastly more people are inapparently infected by one or more dengue viruses. Dengue antibody prevalence studies have not been reported from the Americas, making it impossible to estimate annual dengue infection rates for these areas. In some Southeast Asian countries

annual dengue infection rates have been conservatively estimated at 10%. If this rate is applied to the at-risk population of children less than 15 years old in South and Southeast Asia, approximately 732.1 million^a, then as many as 73 million children may experience at least one dengue infection each year. A substantial but unknown portion of adults is susceptible to dengue. If Asian dengue infection rates are applied to the under-15-year-old populations of all South and Central American countries, 166.6 million (UNICEF Annual Report, 1995), then another 17 million dengue infections occur annually. This estimate does not allow for homotypic or heterotypic immunity, nor are dengue infections in adults estimated. Thus, 50–100 million dengue virus infections occur annually, and not 50–100 million dengue fever cases as often claimed.³³

Dengue is rarely reported from Africa, although infections occur there.^{8,15,16,34} As an explanation of the absence of disease in indigenous Africans, a 1997 seroepidemiological study of children of African ancestry living in Haiti showed high prevalence of dengue antibodies to all four types of prevalence without any recognized dengue disease.³⁵ These results suggest that blacks are genetically resistant and seldom express severe dengue illness and may only experience milder syndromes when infected.

Cost

Only a few local or country-level estimates have been made of the cost incurred by dengue, principally DHF. Estimates in Puerto Rico,³⁶ placed losses at US\$8 million for a population of 2.5 million; in Cuba the 1981 DHF epidemic cost US\$103 million,²⁴ including the cost of control measures (US\$43 million), medical care (US\$41 million), costs of lost productivity (US\$14 million), and loss of salaries of adult patients (US\$5 million) for 344,203 patients. Two outbreaks in Thailand, in 1976–77 and

^a Data from 1993 global population estimates, UNICEF Annual Report, 1995. Included are the under-16-year-old populations of China (only 30% living in the southern provinces), Vietnam, the Philippines, Cambodia, Laos, Thailand, Malaysia, Singapore, Indonesia, Myanmar, Sri Lanka, Bangladesh (dengue endemicity not well documented), India (dengue endemicity not known in detail) and Pakistan (dengue endemicity not well known).

1994, cost US\$7 million²³ and US\$51 million,³⁷ respectively. In Vietnam, during the 1998 epidemic (234,866 cases; 383 deaths), the total direct patient costs exceeded US\$2 million (US\$9 per case). The government spent another US\$1 million on a national antidengue mosquito control program. To obtain some perspective, the US\$3 million allocated for curing or preventing DHF/DSS is borne in a country in which the per capita gross national product is US\$365.³⁸

The most comprehensive method for estimating costs associated with dengue illnesses of all degrees of severity employs disability-adjusted life years (DALY's).³⁹ DALY's were used to assess the burden of dengue in Myanmar, resulting in an estimated 83.8 DALY's lost due to dengue per year per million population from 1970 to 1997.⁴⁰ In Puerto Rico from 1984 to 1994, the economic burden due to dengue, estimated to be 658 DALY's per year per million population, was found to be as important as that for tuberculosis, sexually transmitted diseases (except HIV/AIDS), and the cluster of tropical diseases or intestinal helminths.⁴¹ A household- and population-based study in Thailand found that out-of-pocket costs to families in rural Central Thailand were US\$24, while 426.9 DALY's per year per million population were lost due to DF or DHF.⁴² Other studies have estimated the cost of Thai government subsidies to hospitals at US\$38.65–US\$54.60 per DHF case.³⁷ A 2001 World Health Report attributed 241.6 DALY's per year per million population to dengue for all SE Asian countries.⁴³ All DALY calculations use a multiplication factor of at least 10 on the assumption of underreporting. For severe disease in countries with strong epidemiological services, this degree of underreporting is likely to be off the mark. Milder disease certainly is underreported. The conclusion from all these studies is that costs attributed to dengue illnesses are in the range of the tropical diseases cluster (schistosomiasis, leishmaniasis, trypanosomiasis, onchocerciasis and filariasis).

In order to estimate the full economic impact of dengue illness, in 2005–2006, a single protocol study was conducted in five countries in the Americas (Brazil, El Salvador, Guatemala, Panama, and Venezuela) and in three Asian countries (Cambodia, Malaysia, and Thailand) (personal communication, Dr. Jose Suaya). Participants were patients with suspected or confirmed dengue treated at hospitals or ambulatory facilities, each of whom were interviewed on one to two occasions, medical records

were abstracted, and medical cost data were obtained from facility budget, reimbursements, and utilization statistics. The study estimated the cost per treated case of dengue and made extrapolations based on the 2001–2005 dengue cases and deaths reported to the World Health Organization. Cost calculations consisted of direct medical costs (public and private sector ambulatory and inpatient care), non-medical costs (e.g. transportation, extra food expense), and indirect costs (e.g. days lost by patient and other household members from school, work, or other activities). Costs were expressed in 2005 international dollars (I\$) to adjust for purchasing power parity across countries. Overall mean costs were I\$514 and I\$1394 per ambulatory and hospitalized case, respectively. Mean ambulatory costs varied by country ranging from I\$158 (Guatemala) to I\$699 (Brazil) and hospital costs from I\$752 (Guatemala) to I\$2182 (Thailand). Shares of direct medical, direct non-medical, and indirect costs were 23%, 5%, and 72%, for ambulatory patients and 68%, 9%, and 23% for hospitalized patients, respectively. The distribution of shared costs varied between countries and age groups. Costs for unconfirmed and confirmed cases did not differ significantly within countries or between adults (> 15 years) and children (< 15 years). For the period 2001–2005, the annual average cases and deaths reported in these eight countries were 574,000 and 399, respectively. The corresponding aggregate annual economic cost of these cases and deaths was estimated to be above I\$587 million. If adjustment for under-reporting of dengue were included, this cost could increase to I\$1.8 billion.

Another burden imposed by dengue is the nationwide attempts to control populations of the mosquito, *Aedes aegypti*. In the modern era only two countries, Singapore and Cuba — both islands — have successfully controlled this mosquito. The Ministry of the Environment (Singapore) reported evidence that the house index has been held below 1% for more than 30 years. This success has produced a generation of children with little or no exposure to dengue. But the program increased the political damage caused by continuing dengue cases. Infections among Singaporeans are due to viruses imported from adjacent or trading countries, all of which have hyperendemic dengue.

WHO and the Pan American Health Organization reported that in most tropical countries, *Aedes aegypti* control programs grind on endlessly,

seemingly without any benefit. In Brazil, annual expenditures on dengue control have exceeded US\$600 million, constituting 1.6% of the total health budget. In Thailand, despite annual expenditures reported by the Ministry of Health on the order of US\$11 million, in 2001 the country suffered its largest-ever DHF epidemic.

The DALY method does not describe the fear, disruption and political turmoil caused by epidemics of an urban-based capricious fatal infectious disease. Dengue epidemics have caused considerable political upheaval. An appropriate measurement tool must reflect social disruption costs of dengue.

History

Evolution of dengue viruses

Evidence suggests that the human dengue virus evolved as a parasite of subhuman primates.¹² Animals infected with the ancestral dengue virus must have become separated for prolonged periods, permitting the evolution of viruses whose envelope proteins differed sufficiently to escape cross-neutralization — hence the four virus types. The probable spread from Africa during historical times of *Aedes aegypti* throughout the world created an ecologic niche permitting an urban transmission cycle.^{44,45} Genetic evidence from the few strains studied suggests that the four sylvatic virus types were independently imported into the urban cycle within the past 1000 years,¹² and from ecological evidence this may have occurred in tropical Asia.

Dengue fever

Only after the isolation and characterization of dengue viruses during WWII was it possible to attribute past outbreaks to dengue viruses. While dengue-like disease may have been described in accounts written in China in 992 and the West Indies in the 1600's, without a detailed clinical picture it is hazardous to attribute these outbreaks to dengue.¹⁶ Yellow fever and quite possibly dengue viruses were imported into the New World in the 1600's and the chikungunya virus in 1827–8 as a consequence of the

African slave trade. The first account of a well-characterized clinical syndrome that bears the hallmarks of dengue is that of Benjamin Rush,⁴⁶ who cared for patients during a 1780 Philadelphia outbreak. He noted that the August–September febrile exanthem was confined to persons residing along the Delaware River waterfront. Rush reported a sudden onset with “pains in the head...sometimes in the...eyeballs.... A few complained of the flesh being sore to the touch...nausea universally, and...vomiting, accompanied by a disagreeable taste in the mouth...a rash often appeared on the third and fourth days.... Most of those who recovered, complained of...a total want of appetite.... But the most remarkable symptom (post-illness) was an uncommon dejection of the spirits...one (patient) aptly proposed...to change the name of the disorder to *Break-heart fever*.” There is only one etiology known to produce this constellation of acute phase and convalescent symptoms — the dengue virus.

Rigau-Perez found that the term “breakbone fever” (*quebranta huesos*) was in use in Spain at about the same time as the Philadelphia outbreak.⁴⁷ Outbreaks surmised to be of dengue etiology based upon similar clinical and epidemiological features were common in North America during the 18th and 19th centuries along the Atlantic coast, on the Caribbean islands and in the Mississippi basin.³ Dengue viruses were almost certainly the cause of the five- and seven-day fevers that afflicted European colonists in tropical Asia during the same period.²⁶ Similar diseases occurred among settlers in tropical Australia.¹⁴

Observations that culminated in the recognition of dengue as an arthropod-borne agent were initiated in Lebanon in 1902.⁴⁸ *Aedes aegypti* mosquitoes were first identified as dengue vectors by Bancroft.⁴⁹ This was confirmed and substantiated by the classical studies of Cleland, Bradley and McDonald,⁵⁰ Chandler and Rice,⁵¹ Siler *et al.*³ and Simmons *et al.*⁵ Ashburn and Craig,⁵² using human volunteers, demonstrated that the etiological agent of dengue was present in the blood of patients and that it passed through a Lilliput diatomaceous earth filter. Working in 1922 and 1929, respectively, Siler *et al.*³ and Simmons *et al.*⁵ serially transferred dengue viruses to US Army volunteers by the bite of *Aedes aegypti*. For each of these strains, they identified an intrinsic incubation period in human beings of 3–8 days and an extrinsic incubation period in mosquitoes of 8–11 days. They also documented postinfection immunity in

people and monkeys, and the unsusceptibility to dengue infection of most domestic animals. From neutralizing antibody studies of sera from these volunteers bled in 1973, viruses were identified as dengue types 4 and 1, respectively.⁵³

The modern era of dengue research began in 1943–44, when dengue viruses were recovered in the laboratory following the intracerebral inoculation of suckling mice.^{54,55} Failure of strains to cross-protect in human volunteers led to the designation of dengue viruses types 1 and 2.^{56,57}

Other viruses

Using historical accounts, the etiology of febrile exanthems can easily be confused. The most dramatic mix-up seems to have been caused by a virus known now as chikungunya, an alphavirus in the *Togaviridae* genus. Chikungunya derives its name from the Makonde word meaning “that which bends up,” referring to the characteristic symptom, arthralgia.⁵⁸ An account cited for many years as the initial description of dengue fever was, in fact, probably on chikungunya. David Bylon,^{59,60} “*stads chirurgyn*” of Batavia (Jakarta), described an epidemic of a febrile disease with an acute onset and joint involvement in 1779. Dr. Bylon, who himself contracted the illness, wrote that “it was last May 25, in the afternoon at 5:00 when I noted while talking with two good friends of mine, a growing pain in my right hand, and the joints of the lower arm, which step by step proceeded upward to the shoulder and then continued onto all my limbs; so much so that at 9:00 that same evening I was already in my bed with high fever....” “It’s now been three weeks since I...was stricken by the illness, and because of that had to stay home for 5 days; but even until today I have continuous pain and stiffness in the joints of both feet, with swelling of both ankles; so much so that when I get up in the morning, or have sat up for a while and start to move again, I cannot do so very well and going up and down stairs is very painful.”...“Natives, Chinese, slaves; no race escaped, as both sexes, children, adults and old people were all affected equally; not only in this city of Batavia, but also in the surrounding area.” Remarkably, in 1779 in Cairo and Alexandria, another outbreak occurred of a disease that bears close resemblance to chikungunya fever.⁶¹ Pandemics of a chikungunya-like syndrome were reported from India in 1824–25,

1871–72, 1923, 1964–65 and 2005–07. The latter two epidemics have been virologically identified as being due to the chikungunya virus.^{62,63}

Introduction of the term “dengue”

An interesting pandemic of “dengue” (likely chikungunya) occurred in the years 1870–73, appearing first on the coast of East Africa, then on the Arabian coast and at Port Said.^{3,64,65} From there the disease was carried by emigrant steamers to Bombay, Calcutta, and to Java. The 1870 outbreak led to the discovery that the Swahili word for the disease was “*ki-dinga pepo*”.⁶⁴ “*Pepo*” is derived from the Swahili — “to sway, reel, stagger or totter”.⁶⁶ “*Ki*” is a diminutive. Modern usage of “*dinga*” or “*denga*” in Swahili does not explain the term “*ki-dinga*.” Christie⁶⁴ noted that the term “*denga*”, or “*dyenga*,” had been used to designate the disease in East Africa in an earlier outbreak in 1823 and in the similar disease occurring in the West Indies in 1827–28.⁶⁵ It must be assumed that the chikungunya virus spread to the Caribbean with the African slave trade carrying along its Swahili name and was known locally by various homonyms. It was only after the 1828 outbreak in Cuba that the Spanish word “*dengue*” came into general use in the medical literature, continuing to this day.¹⁵ The term “dandy fever” — a homonym of “*dyenga*” with an apt meaning — was used in English colonies, from where it entered the English medical literature.⁶⁷ There is no evidence that chikungunya was ever imported into the American hemisphere after 1827–28. Over time, the syndromic term originally applied to chikungunya illnesses came to be associated with those caused by the dengue viruses. There are written records of the use of “dengue” to describe an illness occurring among members of the Spanish Court in 1800.⁴⁷ This early usage might still have an African origin, as there were extensive Spanish connections with Africa over many centuries of trade and exploration.

Meaning of “dengue”

When Sabin¹⁹ inquired into the etymology of “dengue,” the standard dictionary meaning of the word was “affectation.” Dengue researchers

were unable to make a connection between this term and characteristic symptoms and signs of dengue. However, an interesting connection does exist — but with *chikungunya*, not dengue. Contemporary observers were struck by the postillness arthralgia and disability caused by “dengue.” Dumaresq⁶⁸ noted: “A person on the disappearance of this fever would attempt to rise from the bed, feeling not much loss of strength, and a consciousness of being able to move about and attend to a little business; but how egregiously would he be mistaken when he assumed the upright posture! The joints felt as if fettered or ankylosed...the appearance of persons in the streets and everywhere else must have been truly pitiable...here one would be seen dragging his legs after him, supported on crutches; and there another with limping gait and various contortions of countenance.” Stedman⁶⁷ noted an even more extreme manifestation of dengue “It is even said that when the disease first appeared in St. Thomas, several negroes, who, being all at once attacked with pain in the knees, had fallen down, were actually apprehended by the police for drunkenness.” Lehman,⁶⁹ Lazaretto physician to the port of Philadelphia, interviewed a ship captain from Cuba who averred “It [dengue] is a vulgar phrase, and implies a ‘staggering weakness,’ and is somewhat similar in its import to our term of ‘corned’ [drunk] as applied to a man reeling about from intoxication.” A modern Spanish dictionary defines the colloquial meaning of “dengue” as “strut, swagger.”⁶⁶ While the African etymological origin of “*dinga*” is still not understood, the original meaning of “*ki-dinga pepo*” was consistently maintained from Swahili to Spanish and seems an apt name for a disease that produces postillness “staggers.”

Dengue hemorrhagic fever

From 1897 to 1902 in Australia, in 1928 in Greece, and in 1931 in Taiwan, a severe syndrome characterized by shock, hemorrhagic manifestations and death was described during dengue epidemics.^{14,70–72} These early outbreaks suggest that DHF/DSS is not a new phenomenon, contradicting the hypothesis that DHF is caused by newly acquired genetic and phenotypic changes.⁷³

Australia, 1897

During the summer of 1897, the inhabitants of the coastal towns of North Queensland suffered their fourth consecutive annual visitation of dengue fever. The unusual virulence of that epidemic engaged the attention of Dr. F. E. Hare of Charters Towers, who undertook to write a general description of the outbreak by polling physicians practicing in the region.⁷⁰ From 19 correspondents Hare obtained records of 60 fatalities, 30 of these in children. The severe illness in children was most characteristic. Hare remarked that these cases were “amongst the most startling that occur in medical practice. In nearly all of these [children] death must be, I think, attributed to the intensity of uncomplicated disease.... All...were previously healthy children; their ages varied between 3 and 14 years...the manner of death was in the majority almost identical, very rapid heart failure and collapse [which] occurred at the crisis on the fifth day of fever, and death ensued from two to 48 hours later.... The patient exhibits all the signs of acute hemorrhage, jactitation (i.e., a frightful restlessness), extreme irritability of temper... terminating (sometimes) in a state exactly resembling the (shock) stage of cholera.” This is a remarkably accurate description of dengue shock syndrome (Chap. 5). It is notable that a small number of DSS-like deaths occurred in an outbreak in which thousands of adults and children experienced classical dengue fever syndrome. Hare himself noted that “large numbers [of persons] who had had the disease two years previously were again attacked equally as badly or even more severely.” It should be noted that the youngest death in this series was a three-year-old child, old enough to have experienced an infection during the 1895 dengue epidemic.

Greece

During 1927, in refugee-swollen Athens and Piraeus, there was a barely perceived mild dengue fever outbreak. This was succeeded in 1928 by the most explosive and virulent dengue epidemic ever recorded.⁷⁴ In August and September alone, there were over 650,000 cases, with 1060 deaths.⁷¹ Retrospective serological studies undertaken using the relatively nonspecific hemagglutination-inhibition test suggested that only a single dengue

virus, type 1, caused the 1927–28 dengue epidemics. Papaevangelou and Halstead⁷⁵ found dengue type 1 and type 2 monospecific neutralizing antibodies and dengue 1 plus 2 antibodies in the majority of individuals who had lived in Athens during the outbreak. A subsequent study of 111 residents of Athens born in 1927, 1928 or in 1931–35 demonstrated predominantly monotypic DEN 1 and DEN 2 antibodies in individuals who were children during the 1927–28 epidemic, but no dengue antibodies in persons born after 1930.⁷⁶

The epidemiological circumstances of dengue transmission in Greece were uniquely favorable for a retrospective serological study. From all available evidence, dengue transmission stopped abruptly after 1928.^{77,78} The epidemics of 1927 and 1928 can be attributed largely to a huge increase in breeding habitats for *Aedes aegypti*. These were created by the need to store water because of a severe water shortage in Athens and Piraeus. This was exacerbated by the large number of temporary shelters erected to house many of the 1.5 million refugees repatriated from Turkey following the Greco-Turkish war of 1922 and the 1923 Treaty of Lausanne.⁷⁹ After 1928, a sustained period of refugee resettlement, the opening in Athens of a municipal water system with a capacity of 40–50 gallons per capita per day⁷⁹ and mosquito abatement ended dengue transmission permanently. Since 1935, there have been few records of *Aedes aegypti* in the Eastern Mediterranean.⁸⁰

Taiwan

Japanese physicians in Formosa described a few fatal cases among children hospitalized in 1931 whose signs and clinical course suggest DSS.⁷²

Post–World War II

Modern DHF pandemic

A comparative lull in reports of dengue activity followed the withdrawal of major foreign forces from tropical Asia at the end of the War. This lull was broken in the mid-1950's by the unexpected recovery of dengue viruses from a "hemorrhagic fever" of children.⁸¹ Hammon, who was in the Philippines to study poliomyelitis, isolated two dengue virus types new to

science, calling these dengue 3 and 4.⁸² Two years later, Hammon and coworkers again recovered dengue viruses from similar cases among children in Bangkok, Thailand, labeling these dengue 5 and 6.⁸³ The “new” syndrome described in Manila, the Philippines, in 1954 was called Philippine hemorrhagic fever, because of clinical similarities to epidemic hemorrhagic fever on the Korean peninsula.⁸⁴ Retrospectively, records at Bangkok’s Siriraj Hospital documented children with DSS-like syndromes during every rainy season from 1950.⁸⁵ Often, these cases received the final diagnosis: “thrombocytopenic purpura with cardiovascular collapse.” When the same reviewers examined 572 pediatric charts from Siriraj Hospital for July and August, 1932–1942, no DHF/DSS-like cases were found.

Causal hypotheses

First impressions, 1958–62

In Thailand, there was a complication. A significant fraction of all hospitalized cases were caused by chikungunya, an alphavirus. Many patients with “Thai hemorrhagic fever” had simultaneous serological responses to dengue and chikungunya viruses. The immediate question was “Why were dengue and chikungunya viruses suddenly causing a severe and fatal disease?”

Early observations resulted in four hypotheses the causation of hemorrhagic fever:

- (1) “*Hemorrhagic variants*,” specifically dengue types 3–6, were responsible;
- (2) *Role of chikungunya*. In Thailand, as opposed to the Philippines, chikungunya, a nondengue virus, seemed to be causing up to 20% of cases. One idea was that simultaneous infections with dengue and chikungunya might account for severe disease.⁸⁶ It seemed possible that the chikungunya virus might have gained virulence since freshly isolated strains produced hemorrhagic enteritis in suckling rodents.⁸⁷
- (3) *Immune response*. The very first serological studies produced evidence that many patients with Thai and Philippine hemorrhagic fever (THF and PHF) experienced extremely high antibody responses to dengue viruses. This suggested that patients had been infected previously with

- an antigenically related virus. Because not all viruses circulating in these countries were known, initial earlier infection could only be guessed at.
- (4) *Human genetic factor*. During the 1962 epidemic in Thailand, predominantly Caucasian expatriates, both children and adults, suffered dengue fever, but not THF.⁸⁸ It seemed possible that Caucasians were genetically resistant to severe dengue disease.

Confusion, 1963–65

Observations made in 1963 and 1964 were helpful, but sometimes contradictory. Dasaneyavaja and coworkers⁸⁹ reported that the chikungunya virus had not been isolated from shock or fatal THF cases. And, because THF and PHF were clinically similar and the chikungunya virus did not occur in the Philippines, it seemed unlikely that chikungunya was a necessary component of the etiology of hemorrhagic fever. As to genetic factors in the host, Halstead and Yamarat⁸⁵ called attention to earlier episodes of severe and fatal hemorrhagic fever associated with dengue fever outbreaks among Caucasians in Australia and Greece. They concluded that Caucasians were not genetically resistant to hemorrhagic fever. They reasoned that failure of Thai dengue strains to cause hemorrhagic fever in Caucasians infected with dengue viruses could only be interpreted to mean that dengue viruses were not inherently virulent. A factor “somehow acquired through continuous exposure to environmental or immunologic conditions of Bangkok”⁹⁰ seemed more plausible. Halstead and Yamarat⁸⁵ called attention to a small THF outbreak in 1964 in which primary-type antibody responses seemed to predominate. At the 1964 WHO conference, Hammon formulated an “immunological response” hypothesis about THF but, after deliberation, discarded it in favor of the virus virulence hypothesis.⁹¹

Increasing clarity, 1966–67

The WHO Seminar on Mosquito-borne Haemorrhagic Fevers held in Bangkok, 19–24 October 1964, was notable for two events — the introduction of the term “dengue hemorrhagic fever (DHF)”⁹² and an agreement that better case definition would improve etiological classification.

This was soon accomplished. In 1966, Cohen and Halstead⁹³ published the classical description of the dengue shock syndrome, describing fully the central underlying pathophysiology as being due to the leakage of fluid and protein through damaged capillaries. This and other work in Bangkok led to the introduction of logical principles of resuscitation. Focussing on dengue shock syndrome (DSS) cases led to a breakthrough on etiology. Halstead *et al.*⁹⁴ found a strong correlation between secondary-type dengue antibody responses and cases with DSS. Analysis was strengthened by new methods in immunology that made it possible to reliably distinguish primary and secondary dengue antibody responses by their association with different immunoglobulin types.⁹⁵

Sequential infections

When multiple dengue virus serotypes are in circulation, solid evidence, for an etiologic role of infection sequence can be obtained by comparing the prevalence of secondary-type antibody responses among DHF/DSS cases with that in milder dengue illnesses. Two important conditions apply: cases must (1) demonstrate clinically significant vascular permeability and (2) be one year of age or older.⁹⁶ The special category of infants DHF/DSS is discussed at length in Chap. 7.

Analysis of antibody responses during DHF/DSS cannot directly answer the question whether severe disease was associated with a second, third or fourth dengue infection. Very few DHF/DSS cases were hospitalized early enough during illness for acute phase sera to retain preillness attributes. An attempt to solve this problem was made by comparing Bangkok age-specific DHF/DSS hospitalization rates with age-specific rates of second, third and fourth dengue infections generated by a mathematical model.⁹⁷ Only second dengue virus infection curves fit DHF/DSS hospitalization data.

It was obvious that only if children were followed from their first through successive dengue infections could it be determined if a second, third or fourth infection resulted in DHF/DSS. Pioneer studies were conducted on Koh Samui island, Thailand, in 1966 and 1967,⁹⁸⁻¹⁰⁰ DHF/DSS cases were shown to occur only in children who circulated dengue HI antibodies prior to onset of severe disease. The HI test method used could

not accurately answer the question whether any of these children had experienced one or more prior dengue infections. The answer required the neutralization test. Many years were to pass before direct evidence for the etiological importance of a single dengue infection was gathered. These data are summarized in Chap. 7.

Immune enhancement, 1968–77

Immune enhancement of dengue virus replication was described *in vitro* and *in vivo* in 1973. Increased growth of dengue 2 virus was observed in cultures of peripheral blood leukocytes (PBL's) obtained from dengue-immune rhesus monkeys.¹⁰¹ Enhanced levels of viremia were observed in rhesus monkeys during second infections as compared with initial dengue 2 infections.¹⁰² It was not immediately evident how “immune enhancement of dengue virus infection” worked. It seemed possible that viruses might replicate in memory T lymphocytes transformed by dengue antigen into lymphoblasts. At the time, it was known that several viruses could grow in phytohemagglutinin-transformed T lymphoblasts.¹⁰³

Antibody-dependent enhancement, 1977–present

Epidemiological evidence had identified two groups at risk of DHF/DSS: children experiencing second dengue infections and infants born to dengue-immune mothers who developed DHF during their first dengue infection.⁹⁶ The only plausible immunological factor that could tie together these observations was antibody. Dengue antibody somehow modulated subsequent infection. Very quickly, it was found that dengue antibody at nonneutralizing concentrations enhanced dengue viral growth in cultures of human and rhesus peripheral blood leukocytes.¹⁰⁴ Mononuclear phagocytes specifically supported dengue virus replication *in vitro* and permitted enhanced infections in the presence of infectious immune complexes.¹⁰⁵ Optimal conditions for *in vitro* infection enhancement were described.¹⁰⁶ Finally, enhancement of dengue 2 viremia was achieved in rhesus monkeys that had been inoculated with small concentrations of passively transferred human dengue antibody.¹⁰⁷ Other laboratories began to study “antibody-dependent enhancement (ADE)”.¹⁰⁸

Confirmation in humans

In a small study, somewhat higher viremias had been demonstrated in a few humans during secondary compared with primary dengue 3 infections.¹⁰⁹ More recent formal studies have demonstrated that viremia titers correlate with disease severity during secondary dengue infections. Peak viremia titers correlated with subsequent disease severity in Thai children experiencing a secondary dengue 2 infection.¹¹⁰ This study is unique, in that viremia titers were measured in successive bleedings starting early in the course of infections. These same children circulated nonstructural protein 1 (NS-1) at levels that correlated with and predicted disease severity.¹¹¹ NS-1 is released from dengue-infected cells and its blood concentration is thought to reflect total cellular dengue infection. A correlation between viremia and disease severity was also found in Thai children experiencing dengue 3 infections.¹¹² Finally, it was observed in Taiwanese patients that dengue RNA titers even after defervescence correlated with disease severity.¹¹³ The contemporary ADE hypothesis of DHF/DSS pathogenesis assigns preillness dengue antibodies an enhancing or neutralizing (afferent) role that up- or down-regulates dengue infection of mononuclear phagocytes. An efferent role (elimination of infected cells) is played by T-cell-mediated immunity. This process produces cytokines that mediate both vascular permeability and abnormal hemostasis by mechanisms discussed in subsequent chapters.^{13,114}

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