



Review

Dengue and dengue-like outbreaks in the past: The case of the Macau epidemic fever of 1874

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ABSTRACT

Historical sources abound in references to outbreaks of a disease resembling dengue fever. Medical observers reported on its rapid onset and great expansion in the population, the diversity and changeability of its clinical features and its overall mildness. In 1874, an epidemic disease with fever, rash and rheumatic pains as main symptoms broke out in the Portuguese colony of Macau, South China. It was similar to the epidemic disease which swept the colony 2 years before during the so-called dengue pandemic of 1870–1873. The 1874 epidemic disease was variously labeled by local physicians, including dengue fever. In his report on the disease, Dr. Lúcio Augusto da Silva, hence at the head of the health services of Macau, discussed on the nature of the epidemic febrile disease. Here, I review the data on the 1874 epidemic outbreak and put them in the context of historical dengue-like outbreaks. A possible Chikungunya etiology of the disease is postulated.

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1. Introduction

In 1872, during the so-called dengue pandemic of 1870–1873, an epidemic disease with fever, rash and rheumatic pains as main symptoms broke out in the Portuguese colony of Macau, South China. It swept again the locality 2 years later and affected the majority of the population, natives and foreign residents alike. As

in 1872, it was variously diagnosed by local physicians, including rheumatic roseola, rheumatic miliar, eruptive and rheumatic fever, intermittent fever and articular rheumatism and dengue fever. The 1874 epidemic disease formed the subject of a special report¹ by the chief of the health services of Macau, Dr. Lúcio Augusto da Silva. In this report, the Portuguese physician examined the epidemiological and clinical data of the epidemic disease and discussed the

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¹ da Silva (1880). Duas Palavras sobre a Dengue. Relatório do Serviço de Saúde Pública na Cidade de Macau Relativo ao Anno 1874. Typographia Mercantil, Macau.

diagnosis of dengue given by one physician. He concluded that the so-called dengue was the hybrid manifestation of distinct eruptive fevers in their rheumatic form. Medical data of the Macau epidemic febrile disease were reexamined in 1886 by the new chief of the health services of the Portuguese colony, Dr. José Gomes da Silva, who concluded that dengue was a form of roseola (da Silva, 1887). The article reviews the data on the 1874 epidemic febrile disease, putting it in the context of historical dengue-like outbreaks. The historical review illustrates the difficulty physicians had in establishing a differential diagnosis. This same difficulty is apparent in the various diagnoses given by local physicians to the Macau outbreak. An alternative etiology is postulated for the disease.

2. Natural history and clinical features of dengue fever

Dengue fever [DF] is currently one of the most widespread arbovirus diseases in the world. It is endemic in many tropical and subtropical regions in Africa, the Americas, the Caribbean, the eastern Mediterranean, Asia and the Western Pacific. It is estimated that 2, 5 billion people incur the risk of infection and that the dengue virus infects annually about 100 million people around the world, 500,000 of them will develop the severe form known as dengue hemorrhagic fever (Gubler, 1997; Halstead, 1997; Vasilakis and Weaver, 2008). Though it is rarely fatal in its mild form, the disease has severe socio-economic and environmental consequences in endemic areas: In 2001, for example, the reported number of disability-adjusted life-years (DALYs) lost to dengue was globally 528 (Cattand et al., 2006; WHO, 2009a).

Dengue fever is caused by a virus [DENV] of the genus *Flavivirus* (Family *Flaviviridae*) of which four phylogenetically distinct serotypes have been identified so far: DENV-1, DENV-2, DENV-3 and DENV-4. They are widely distributed in tropical and subtropical regions of the world, responsible for endemic/epidemic dengue and they produce a similar disease of varying severity in humans. DENV-1 was first recovered by Kimura and Hotta from the blood of dengue patients injected intra-cerebrally into mice during the 1943 epidemic outbreak in Nagasaki, Japan (Kimura and Hotta, 1944; Hotta, 1965). DENV-1 and -2 were subsequently isolated from US soldiers during World War II whereas DENV-3 and -4 were isolated in 1954 from patients during an epidemic of dengue hemorrhagic fever in Manila, Philippines (Sabin and Schlesinger, 1945; Sabin, 1952; Hammon et al., 1960). Infection with a given serotype confers a lifelong immunity to it but only a short-term cross-protective immunity to the other serotypes (WHO, 2009a, 2011). For example, during the outbreak of dengue fever in Santiago de Cuba in 1997 caused by a Southeast Asian genotype of DENV-2, almost all adults immune to DENV-1 fell ill and developed an illness varying from classical dengue to dengue hemorrhagic fever (Halstead, 2008). Different serotypes may be involved in the same epidemic as it happened in 1976/77 during the dengue outbreak in Jakarta, Indonesia (see Discussion Gubler in Holmes, 2006). Each serotype may be subdivided into a variable number of genetically distinct groups (subtypes or genotypes) according to the degree of nucleotide sequence divergence within a given genome region (Rico-Hesse, 1990; cited by Holmes, 2006; Vasilakis and Weaver, 2008). Until now, three genotypes in DENV-1, six in DENV-2, and four in DENV-3 and -4 have been differentiated (WHO, 2011). Unlike virus serotypes, genotypes are heterogeneously distributed throughout the world. Some are specific to certain regions or continents. For example, DENV-2 has apparently two distinct genotypes which are specific to Southeast Asia. Some genotypes are also more virulent and with a greater epidemic potential than others (Twiddy et al., 2002; cited by Holmes, 2006).

Humans are the main known host of dengue virus, with *Aedes aegypti* and *Aedes albopictus* (the Asian “tiger mosquito”) being the primary vectors. Their vector role has been demonstrated through a series of experiments on human volunteers conducted by Bancroft (1906), Cleland et al. (1916), Chandler and Rice (1923) and Simmons et al. (1930).

Dengue virus infection may be asymptomatic or may cause an undifferentiated febrile illness or the disease dengue with varying grades of severity: mild (usually known as classical dengue) and/or severe and potentially life-threatening (dengue hemorrhagic fever [DHF] and dengue shock syndrome [DSS]). Clinical manifestations and grading of severity depend on the virus strain and on factors related to the host such as, for example, age, immune status, secondary infection, and possibly also chronic diseases (diabetes mellitus, sickle-cell anemia, etc.) (WHO, 2011). The incubation period of classical dengue varies from 13 to 14 days. In some cases, the onset of the disease is announced by a prodromal stage characterized by a feeling of general malaise, chilliness, rheumatic-like pains and/or gastric disorders. Disease characteristics include a sharp rise in temperature (up to 40 °C [104 °F]) with relative bradycardia and hypotension, frontal or retro-orbital headache, an eventual rapid and diffuse flushing on the face, neck and chest but more frequent on the face (on the second or third day) and pains in the muscles and bones/joints. Fever and other symptoms usually persist for 48–96 h. Then, fever recedes rapidly through a more or less profuse sweating. In the majority of cases, this is followed by 24 h free from fever during which the patient feels quite well. However, a second rise in temperature occurs accompanied by a maculopapular or rubelliform rash spreading from the extremities to cover the whole body, except the face. The palms and soles of the patient may be red and swollen. In the end or after the defervescence of the fever, the second rash fades away, and confluent petechiae surrounding scattered and pale areas of normal skin may appear on feet, legs, hands and arms. The skin may be itching. Nausea and vomiting may occur between the second and the sixth days of the disease. Some patients manifest sore throat, injected pharynx and conjunctival infection. All these symptoms vary in frequency and intensity. The severity of myalgia and bone pains accounts for the name of break-bone fever which has been applied to the disease in the past.

Bleeding manifestations (epistaxis, gingival or gastrointestinal bleeding, hematuria, and hypermenorrhoea) are unusual. Leukopenia is frequent. Thrombocytopenia and albuminuria may be observed. DF cases with hemorrhagic manifestations must be differentiated from DHF cases which are mainly characterized by high fever, petechiae, ecchymosis or purpura, bleeding manifestations (from mucosa, gastrointestinal tract, injection sites, etc.), hepatomegaly, positive tourniquet test, thrombocytopenia (platelet count equal or inferior to 100,000 cells/mm³), objective evidence of plasma leakage (rising hematocrit, pleural effusions, ascites, etc.) and often signs of circulatory disturbance or failure. The duration and severity of DF vary according to the cases in a given epidemic or from one epidemic to another but the disease seldom proves fatal (the disease case-fatality is less than 1%). The duration of convalescence also varies. In adults, it often lasts several weeks and may be characterized by pronounced asthenia and depression. Furthermore, muscle and bone pains may persist for weeks (George and Lum, 1997; Farrar, 2008; WHO, 2009a, 2011). Atypical clinical manifestations of DF and DHF have been described recently. They may consist in neurological (febrile seizures in children, encephalopathy, encephalitis, etc.), renal (acute renal failure), gastro-intestinal/hepatic (hepatitis, acute pancreatitis, acute parotitis, etc.), cardiac (myocarditis, pericarditis, etc.), respiratory (acute respiratory distress syndrome, pulmonary hemorrhage) and/or ocular (macular hemorrhage, impaired visual acuity, etc.) manifestations indicating a severe organ impairment. They may be a complication

of a dengue shock syndrome or associated with underlying host conditions or with co-infections (WHO, 2009a, 2011).

Nowadays, the presence of fever with at least two other symptoms (anorexia and nausea, headache, rash, arthralgia/bone pains, leukopenia, existence of warning signs such as abdominal pain or tenderness, persistent vomiting, mucosal bleeding, lethargy, etc.) is considered an indicative of dengue fever (WHO, 2009a, 2011). Because of the lack of specificity of dengue clinical features, their apparent fickleness according to individual cases or epidemic outbreaks, and their close resemblance, depending on the period of the disease, with those of other infectious diseases (e.g. influenza, Chikungunya fever, typhus, typhoid fever, leptospirosis, malaria, measles, rubella and other viral exanthems, pappataci (or sand-fly) fever, West Nile fever, etc.), clinical diagnosis must be confirmed through antibody detection and virus isolation (George and Lum, 1997; WHO, 2009a). Laboratory tests became available in the late 1940s.

3. A historical appraisal of dengue and dengue-like outbreaks over the world

Historical sources abound in references to outbreaks of a disease resembling dengue but variously named by medical observers (“*knokkle-koorts* [knee-trouble]”, “break-bone fever”, “bilious remitting fever”, “dandy fever”, “dengue fever”, “inflammatory fever”, “eruptive articular or rheumatic fever”, “three-day fever”, “*scarlatina rheumatica*”, “*fièvre rouge* [red fever]”, “*fièvre chinoise* [Chinese fever]”, “*La Piedosa* [the mild]”, etc.).² It is generally stated that the first description of a dengue-like illness is found in a Chinese medical encyclopedia dating back from the Chin dynasty (265–420 A.D.), first edited in A.D. 610 (Tang dynasty) and again in A.D. 992 (Northern Song dynasty). It mentioned a disease called “water poison” linked to water-related flying insects and characterized by fever, rash, pain in the eyeballs, arthralgia, and myalgia and also by pharyngeal, gingival, vaginal, or intestinal bleeding (Nobuchi, 1979; cited by Gubler, 1997). References to outbreaks of an apparently similar disease were made in the 17th and 18th centuries in the French Indies (1635), Darien (Panama, 1699), Batavia (present-day Jakarta, Indonesia, 1779), Cairo and Alexandria (Egypt, 1779), Philadelphia (United States, 1780) and in Cadiz (1784 and 1788) and Seville (1784 and 1785), Spain, etc.³ The epidemic disease in Philadelphia (1780) described by the physician Rush (1789) is generally considered as bearing all the characteristics of dengue fever. The disease broke out during the summer and autumn (July–October) 1780 and affected all the persons living along the Delaware River waterfront. It was locally called “break-bone fever”. Rush, who labeled it “bilious remitting fever”, described its sudden onset, the high fever with or without a little thirst, the severe pains in the head (sometimes only in the eyeballs), back and limbs or in the neck and arms, the soreness of painful areas, the nausea, the eventual presence of vomiting with a bad taste in the mouth, the emergence of a rash (on the 3rd or 4th day), the eventual burning sensation in the soles of feet and palms of hands, the nose bleeding (on the 3rd or 4th day) or profuse nose, and the mouth and bowels hemorrhages (on the 10th or 11th day) causing death. In several cases, jaundice succeeded to fever. Some patients presented with dysentery. Fever usually receded on the 3rd or 4th day through sweating but it could last for 11 or even 20 days. Relapses were frequent. Convalescents frequently complained of nausea, want of appetite, faintness, weak-

ness in the knees and of an “uncommon dejection of the spirits” (Rush, 1789; see also Carey, 1971).

During the 19th century, scattered outbreaks of a disease resembling dengue were reported in tropical and sub-tropical regions of the world. In 1824, for example, a dengue-like illness struck Calcutta, India. Its characteristics included a sudden onset, violent pains in the head and body parts, facial flush, debility, presence of a rash of variable character, overall mildness of the disease, frequency of relapses and persistence of pains for weeks after the end of the acute phase of the disease (Mellis, 1825; Cavell, 1826). Old inhabitants of the city called it “three-day fever”⁴ (Cavell, 1826). In 1826–1827, an epidemic of “break-bone fever” was reported in Charleston (South Carolina) and Savannah (Georgia), southern United States. A year later, during the summer, an epidemic febrile disease struck again Charleston. Called at that time “dengue”, it shared the main symptoms with the break-bone fever reported in Savannah in 1826–1827 (e.g. great expansion, violent pains in the limbs and joints, variability of the rash, short duration of pains and rash, overall mildness of the disease, etc.) but differed from it by “less debility and less tediousness of convalescence” and also by the longer persistence of pains, mainly in the joints (Dickson, 1829; Waring, 1830; see also Carey, 1971). In 1827–1828, an apparently similar disease was recorded in the islands of St. Thomas and St. Croix, in the West Indies (Stedman, 1828; Ruan, 1829). English-speaking population of St. Thomas’s called it “dandy fever”, an allusion to the stiff gait produced by the disease. The St. Thomas’s “eruptive articular or rheumatic fever”, as Stedman (1828) labeled it, differed from the Philadelphia “break-bone fever” (1780) by the suddenness of the attack, the existence of distinct stages, the scarlet eruption and the nature and duration of the after-pains (Stedman, 1828; see also Carey, 1971). During the 1850s, scattered epidemics of a disease struck the United States (Charleston, S.C.), India (Calcutta), Egypt, Greece, Peru, Brazil, Spain, etc. In 1850, for example, a disease labeled as “break-bone fever” affected 7 to 8 or 10% of the population (e.g. 31,000–36,000 people) of Charleston, sparing no age, sex or class in that fraction of the population (Dickson, 1850; Wragg, 1851). The disease bore some similarity with the Philadelphia “break-bone fever” of 1780 (e.g. rapid onset and spread, great expansion, overall clinical picture) but differed from the previous “dengue” in the locality (1828) by the pains and soreness in the flesh (not in the joints), the varying aspect of the rash, the frequency of hemorrhages, the marked debility of the patient and the fact that it attacked the same individual two or even three times⁵ (Wragg, 1851; see also Carey, 1971).

During the years 1870–1873, a dengue-like outbreak swept over various continents. It started apparently in Zanzibar (July 1870), on the east coast of Africa, then spread to the Arabian coast (Aden, Jeddah, Mecca, Medina, etc.) and to Port Said. From there, it was carried by emigrant steamers to Java and India. It also reached Indochina (Vietnam, Laos and Cambodia), South China, Formosa [present-day Taiwan], Sumatra, and, finally, Mauritius and Reunion islands (Hirsch, 1883). In Zanzibar, where it raged from July 1870 until January 1871, it nearly affected the entire population. Old inhabitants of the locality gave it the name of a disease which had affected them in 1823 (e.g. *kidinga pepo* or “cramp-like pains produced through the agency of an evil spirit”; see Christie, 1872, 1881). In India, the disease struck Bombay, Calcutta, Madras, Dacca, Pondicherry, etc. In Bombay, the first cases of the disease

² For a review of popular and medical denominations of dengue and dengue-like illnesses in the past, see Aitken (1866), Rey (1868), Labadie-Lagave (1873) and Hirsch (1883). Obviously, these different denominations may refer to different diseases.

³ On these various epidemics, see Bylon (1780), Cubillas (1784), Nieto de Piña (1784), Rush (1789), Poggio (1871), Hirsch (1883), and Pepper (1941).

⁴ In the past, dengue fever was often confused with the “three-day fever” (see, for example, Megaw, 1919, 1923). It is now known that this latter disease (also called pappataci or sand-fly fever) is caused by a virus of the Genus *Phlebovirus* (family *Bunyaviridae*).

⁵ This observation is consistent with the current knowledge on dengue fever, the existence of phylogenetically distinct dengue serotypes, their potential simultaneous circulation during the same epidemic and the limited cross-protection between the serotypes.

were observed in August 1871. Gerson da Cunha (1872) reported the abrupt onset, the severe pains in the back, limbs, and in the joints, the latter being accompanied with swelling, the high fever, the appearance of a rash at two distinct periods of the disease (distinction between an “initial” and a “terminal” rash), the variability of the “terminal” rash which was mimicking that of scarlatina or measles or was a mixture of papular, vesicular and/or pustular forms, the various periods of the disease and the persistence of rheumatic pains (particularly in the joints) for months during the convalescence. Shircore, in Calcutta, also mentioned the sudden onset of the disease, the presence of the rash, the rheumatic pains “more articular than muscular” and the persistence of joint pains during the convalescence (Shircore, 1872). The disease affected about 75% of the population. Despite its overall mildness, it was “very painful” (Anonymous, 1872). In Dacca, Wise (1873) reported the variability of individual cases (“no two cases are exactly similar”) which was manifest in the disease onset (with or without prodroma), the location of pains, the time of appearance of the terminal rash or its varied character (pale erythematous spots, urticaria or vesicular eruption) and/or the persistence of pains for more or less time after the acute phase of the disease.

The dengue-like illness reached South China during the second semester of 1872. It was first noted in Amoy (August), then in Hong Kong (September) and, finally, in Macau (October). In Amoy, the disease was characterized by four well definite stages: a first stage marked by a fever of variable intensity during 1–3 days, myalgia and articular pains, occasional swelling and congestion of the skin, ending by a crisis of sweating, diuresis, diarrhea, or epistaxis; a second stage (from the end of the 4th to the 5th or 6th day) during which the patient was feeling well or was troubled with debility, myalgic pains, or anorexia; a third stage marked by a slight return of fever, an exacerbation of pains, and a skin rash followed, after a day or two, by a diminution of pains, the fading away of the eruption, and, at times, a slight desquamation; and a fourth stage, that of convalescence, of variable duration, during which the patient was troubled with severe pains or slight and transitory attacks of fever (Müller and Manson, 1873; Manson, 1897). First mistaken with measles, the disease was gradually considered as new by local physicians. It affected 95% of the natives and 58 (among the 160) European residents. Its origin in the locality is unclear. According to Müller and Manson (1873), it had probably been imported by returning immigrants from the Straits Settlements where it had been prevailing for months. In Macau, the disease broke out in October 1872 during various works undertaken in the city (earthwork of a hill for the construction of the new military hospital, roadwork, removal of the garbage, etc.). It began to recede in January 1873, when isolated cases of smallpox appeared, and ended in May of that same year, leaving the place to a smallpox outbreak. The number of cases is unknown. The disease was variously diagnosed by local physicians: *roseola rheumatica* [rheumatic roseola], *miliaria rheumatica* [rheumatic miliar], *febre eruptiva e rheumatica* [eruptive and rheumatic fever], *febre intermittente e rheumatismo articular* [intermittent fever and articular rheumatism] and *febre dengue* [dengue fever] (da Silva, 1880).

The dengue-like illness reached Indochina in 1873. In Cochinchina [present-day Vietnam], it was called *cum* which means “hindrance” or “to break the muscles or the tendons”. It seems that isolated cases of a similar disease had been reported before in the region (in 1867, for example) but it was the first time that it broke out in an epidemic form. D’Ormay (1914) noted that the pains were “more muscular than articular” and distinguished two “forms” of the disease: an “eruptive form” more frequent in Europeans and characterized by an “intense coloration of the skin” and a short duration of the pains and a “rheumatic form”, predominant among the Annamese, with a less pronounced coloration of the skin but

with greater violence and duration (lasting eventually for months) of the pains.

Finally, the disease broke out in the islands of Mauritius and Réunion. In St. Denis (Réunion Island), it affected about 20,000 of the 35,000 inhabitants, sparing no age, sex, occupation or ethnic origin. Nine of the 11 physicians and pharmacists of the locality were also affected. Cotholendy described the sudden onset of the disease, the presence of pains in the lumbar region and, above all, in the articulations with concomitant swelling, their different intensity according to the cases, the variability of the initial rash (present in about half of the cases), the cephalgia, the constancy but lack of specificity of the terminal rash, the desquamation, the variable duration of convalescence marked by the general debility of the patient and the persistence of rheumatic pains and, finally, the overall benignity of the disease. However, he cited several cases of death caused by convulsions in young infants and by cerebral or pulmonary complications in elderly people (over 70 years of age) (Cotholendy, 1873).

Outbreaks of an apparently similar disease were also reported over the world during the last decade of the 19th and the first half of the 20th century, for example in Australia (1897–1898, 1905, 1925–1926, 1942–1944, etc.), Japan (1900, 1904, 1915, 1916, 1924, 1927, 1942–1945, etc.), Hong Kong (1901–1902, etc.), Thailand (1901), Malaysia (1901, 1910, etc.), Singapore (1901, 1945, etc.), China (1904, 1940, 1945, 1947, etc.), Myanmar (1901–1902, etc.), India (1901–1902, 1945, 1967, etc.), Indonesia (1910, 1917–1919, etc.), Taiwan (1915–1917, 1922, 1925, 1930, etc.), Philippines (1905–1907, 1910, 1922–1924, 1929–1930), Vietnam (1905, 1907, 1908, 1927), Greece (1927–1928, 1929–1933), Africa (1914–1918, 1927), Egypt (1937), Hawaii (1943–1944, etc.), French Polynesia (1944, etc.), New Guinea (1944, etc.), etc.⁶ The dengue etiology of certain dengue-like events between 1920 and 1950 has been retrospectively confirmed by serological studies (Kuno, 2007, 2009; Van Kleef et al., 2010).

The variety of medical denominations applied to dengue and dengue-like illnesses in the past – which reflects the etiologic uncertainty of the disease-, and the non-existence of confirmatory serological and virus-specific laboratory tests until the late 1940s make it difficult to define their precise nature and establish a definite diagnosis. This review of medical data provides, however, some insights on the epidemiological characteristics of historical dengue and dengue-like outbreaks. Firstly, the disease was said to attack almost everyone without any distinction of sex, age, ethnic origin, occupation, social condition and health state.

Secondly, the diversity of clinical features, including, in particular, the incubation period of variable duration (2–15 days), the sudden onset of the disease or the existence of a prodromal stage (with a feeling of malaise, general weakness, headache, rheumatic-like pains, loss of appetite, chilliness, etc.), the well-marked evolutive stages (2–4 stages have been documented), the rapid rise of fever to 39 or 40 °C, its short duration (3–7 days) and biphasic curve, the presence of a rash at two distinct periods of the disease and the existence of rheumatic and/or articular pains was emphasized by all medical observers.

Thirdly, variations in frequency, time of appearance, clinical presentation, setting, severity and/or duration of main symptoms (e.g. rash and pains) according to the cases, the place and/or the epidemic outbreak, added to the confusion. For example, the initial rash, which was sometimes limited to a red flush of the skin (particularly in the face), could be unnoticed due to its short duration. The terminal rash was usually described as highly varied, likening, according to the cases or the epidemic outbreaks, that of roseola,

⁶ On dengue and dengue-like outbreaks during the 19th and first half of the 20th century, see Rey (1868), Thomas (1881), Hirsch (1883), Leichtenstern (1905), Armstrong (1923), Carey (1971), Kuno (2007, 2009), and Van Kleef et al. (2010).

scarlet fever, rubeola, measles, impetigo or even urticaria. In some cases, it was mimicking the rash of distinct eruptive fevers. Variations were also reported for the pains (preceding or following the first fever, predominance of articular, muscular or joint pains, presence or absence of swellings of the joints, varying intensity, variable duration during the convalescence, etc.). The wide clinical spectrum of the disease and the variability in its main clinical features, which may well explain the difficulty physicians had in establishing a differential diagnosis, led several of them to conceive dengue as a “disease of a variety of types” (Thomas, 1881) or as a “collection of multiple diseases” (see, for example, Cleland et al., 1918; cited by Kuno, 2009).

Fourthly, the disease seldom proved fatal though it could be serious for the feeble or for persons weakened by other diseases who could succumb to the initial fever or to the following debility (see, for example, Christie, 1872; and Müller and Manson, 1873). Moreover, cases of death due to complications were reported in children and elderly people during the 1873 Réunion outbreak (see Cotholendy, 1873).

These characteristics are for the most part compatible with classical dengue fever as it is defined today. It has to be said, however, that the persistence of myalgia and arthralgia long after the acute phase of the disease and the predominance of joint pains (particularly in the small ones) pointed out by some medical observers fit the clinical characterization of Chikungunya fever [CHIK]. This disease is caused by an *Alphavirus* of the *Togaviridae* family which, in Asia, is transmitted by the same vectors as the dengue virus (*A. aegypti* and *A. albopictus*). Rarely life-threatening, CHIK is characterized by an abrupt onset of fever of short duration, headache, skin rash, myalgia, and a severe, chronic and disabling arthralgia (which may persist for months or years), particularly in the small joints of hands and toes. Skin rash is reported in about 40–50% of the cases. It is usually of the pruriginous maculopapular type but other forms can be seen. High fever (up to 40 °C/104 °F) and arthralgia are the most frequent clinical manifestations (WHO, 2009b). A CHIK etiology was thus postulated by Carey (1971) for several historical dengue-like outbreaks, including the Indian outbreaks during the so-called dengue pandemic of 1870–1873.⁷ This hypothesis was, however, recently questioned by Kuno (2009) on the basis that prolonged arthralgia (for 5 or 6 months or even a year) has been found in laboratory-confirmed dengue patients (see, for example, González et al., 2005; Vasilakis and Weaver, 2008; cited by Kuno, 2009). An alternative way to infer the possible etiology of CHIK for some historical dengue and dengue-like outbreaks is to consider the presumed antiquity of the virus of both diseases. Recent phylogenetic studies date the origin of dengue viruses about 1000 years ago (Twiddy et al., 2003; cited by Holmes and Twiddy, 2003; and Holmes, 2007). Moreover, as the four serotypes are present in Asia in both humans and monkeys (Wang et al., 2002; cited by Holmes, 2006), some scholars inferred that dengue viruses may have an Asian origin (Holmes and Twiddy, 2003; Holmes, 2006). With regard to Chikungunya virus [CHIKV], it is postulated that existing strains (e.g. West African, East/Central/South African, and Asian) evolved from a common African sylvatic ancestor that “emerged between 150 and 1350 years ago” and that the African and Asian genotypes diverged in a period ranging from 50 to 430 years ago (Powers et al., 2000). This suggests that CHIKV could have been introduced into Asia at any time within this period. In this case, the possible Chikungunya etiology suspected by Carey (1971) for at least the Indian outbreaks reported during the so-called dengue pandemic of 1870–1873 cannot be discarded.

⁷ According to Carey (1971), for example, the dengue-like outbreaks reported in Batavia (1779), Cairo (1779), Zanzibar (1823 and 1870), India (1824–1825 and 1871–1872), West-Indies (1827–1828), New Orleans and Charleston (1827–1828) were possible cases of Chikungunya fever.

This historical review of medical data illustrates the difficulty physicians had in the past in defining and clinically characterizing dengue-like illnesses. This difficulty is also apparent in the various diagnoses given by local physicians to the Macau epidemic fever of 1874.

4. The 1874 epidemic of dengue-like illness in Macau

Two years after the first visitation of a dengue-like illness in Macau, an epidemic febrile disease with apparently similar symptoms broke out in Macau.

4.1. Characteristics of the 1874 Macau epidemic fever

4.1.1. Season of occurrence, origin and duration

Isolated cases were registered in August and September 1874. These 2 months, which correspond to the summer in Macau, are characterized by a high temperature, abundant rains and more or less frequent storms (da Silva, 1887). During the night of the 22nd–23rd of September, a violent typhoon swept the littoral area of Macau. It destroyed public buildings and houses and killed hundreds of people, mainly among the population living along the littoral or in boats (estimated to 10,000 or 11,000 persons). In order to prevent the emergence of those diseases which frequently follow natural calamities (such as cholera, for instance), the governor of the Portuguese colony adopted various measures: destruction through fire of the cadavers of persons and animals; fumigations of tar in various areas of the city; destruction of spoiled or deteriorated food; removing of rubble, etc. However, the typhoon was soon followed by an outbreak of measles, roseola and of the febrile disease first reported in Macau in 1872. As in 1872, disease cases were variously labeled by local physicians: *roseola rheumatica*, *miliaria rheumatica*, *febre eruptiva e rheumatica*, *febre intermittente e rheumatismo articular* and/or *febre dengue*. Only two disease cases received the appellation of dengue fever. Cases of conjunctivitis, coryza and guttural angina were also registered. They were probably related to the dust saturating the atmosphere after the damages caused by the typhoon. Eruptive fevers and inflammations proceeded in autumn (October and November), a season characterized by a diminution of temperature. They disappeared in December (first month of winter). Numerous patients continued, however, to suffer from arthritic and muscular pains after the acute phase of the disease (da Silva, 1880, pp. 17–19 and 27–30).

4.1.2. Incubation period and prodromal stage

In some cases, the disease had a brutal onset, with no prodromal stage. In others, it was preceded by signs and symptoms such as prostration, general weakness, slight muscular pains in the limbs, headache, want of appetite, etc. (da Silva, 1880, p. 19).

4.1.3. Symptomatology and evolution

The disease had two distinct periods. The first one was marked by the following symptoms: muscular pains of varying intensity in the whole body, being, in some cases, particularly intense in the head, nape and lumbar region and somewhat simulating a stiff neck; pains in the small joints (in several cases, in the great ones too) with accompanying swelling. In several cases, these pains prevented the patient from moving; painful or tingling sensations in the fingertips with extension to the upper arm; rise of temperature (38 to 40 °C) preceded or not by chills. The severity of the fever varied during the course of the disease. It produced a transient red flushing of the ocular-nasal membrane and skin. Occasional thirst and rare cases of nausea and vomiting were noted. Dejections were normal though several cases of constipation were reported.

The pulse ranged between 100 and 120. The aspect of the tongue was normal or slightly covered with a white or yellow coating. Several cases of inflammation of the guttural pouch mucosa and mouth have been noted. The aspect of urine was either consonant with the patient's health state or urine was highly colored, as happens in pyrexia. No albuminuria was noted in the cases where it had been searched for.

The initial fever usually receded in 36–72 h through a slight sweating. For the next 48–96 h and depending on the severity of the disease, patients could stay prostrated; some complained of pains in the limbs; others seemed to be quite well, as if in convalescence, whereas still others looked in a perfect health state.

A second period of the disease was then observed, characterized by a new rise in temperature, although fever was milder than during the first period; a recrudescence of pains (though slighter than those previously noted) with swelling of the small joints; and the presence of a rash which was preceded by a pruritus in the face, trunk, back and extremities. Fever usually decreased completely after 24–36 h. The second rash varied in character, mimicking, according to individual cases, that of roseola, miliar, measles or scarlet fever or it was the mixture of the rash of distinct eruptive fevers. It should be noted that when the initial fever, being of the remittent type, did not recede completely, the second rash appeared only after a distinct febrile paroxysm. It usually began to recede 3 or 4 days later, fading away through a fine furfuraceous desquamation or through small plaques for 1 or 2 weeks. During the convalescence, several patients complained of arthritic and muscular pains for weeks and even months, especially in the small swollen joints or in the articulations of the inferior limbs. In some cases, these pains prevented them from moving (da Silva, 1880, pp. 19–21).

4.1.4. Complications

Cases of epistaxis, convulsions in children, one case of hematuria and various cases of diarrhea were registered. However, as stated by the Portuguese physician, these complications were frequent during periods of intermittent fevers in Macau. Finally, no crisis of abundant diuresis and no profuse sweating were noted (da Silva, 1880, p. 21).

4.1.5. Extension and outcome of the disease

Nearly all the population of Macau was attacked by the disease but no fatal case has been reported. Dr. da Silva attributed the overall benignity of the disease to the fact that it occurred in autumn, the safest season of the year (da Silva, 1880, p. 30).

4.1.6. Methods of treatment

The treatment administered was purely symptomatic. During the first period of the disease, emollient, antispasmodic and/or acidulated drinks were administered to the patients according to their health state; slight purgatives (drink made with cream of tartar, for instance) were given to patients having a tendency to constipation. Chloral hydrate supplemented, in some cases, by liniments made with a local narcotic (unspecified), was used to mitigate muscular and arthritic pains, headache, and insomnia. Quinine was employed to relieve fever. Taken in small doses, it appeared to shorten the febrile period.⁸ Used as a prophylactic for 3 or 4 days, it prevented the development of the disease in patients presenting with prodroma, a fact Dr. da Silva experienced himself.

In a few cases, the second rise of the fever was left untreated due to its short duration. In others, the treatment described above was used, with the exception of quinine. Bromated potassium,

alternatively with quinine, was administered in case of convulsions. Cases of diarrhea were treated with sub-nitrate of bismuth simples or associated to calcium carbonate and, in certain cases, to pepsin. Frictions with a solution of iodide of potassium supplemented, in some cases, by a few drops of Sydenham's laudanum were used to relieve the pains after the acute phase of the disease. When treatment fails, pills of colchicum extract, quinine and digitalis were administered to the patient. These were the main remedies used by the Portuguese physicians during the epidemic outbreak. Finally, numerous cases were treated by family remedies and, hence, escaped the attention of local physicians (da Silva, 1880, pp. 30–32).

5. Discussion and conclusion

In his discussion of the nature of the epidemic febrile disease that struck Macau in 1874, Dr. Lúcio Augusto da Silva emphasized the varied character of the terminal rash and concluded that the disease called dengue by a local physician was not a distinct nosological entity but the hybrid manifestation of different eruptive fevers in their rheumatic form (da Silva, 1880, pp. 22, and 25–26). A few years later, the new chief of the health services of the Portuguese colony, Dr. José Gomes da Silva, re-examined the data on the epidemic outbreak of 1874. Arguing the fact that he had never observed in his clinical practice in Macau the rheumatic pains and swollen articulations described by Dr. Lúcio Augusto da Silva and other medical observers, he concluded that the so-called dengue fever "is no more than the rheumatic roseola of Neumann, a variety of the symptomatic roseola of Alibert" (da Silva, 1887, p. 54). To better understand this last observation, it is necessary to briefly review the definition of roseola by Alibert and Neumann. According to the French dermatologist J.L. Alibert (1768–1837), the symptomatic roseola (*roseola symptomatica*) is a fugitive exanthem which is often "the expression or the result" of other diseases (Alibert, 1833). In this, it differs from the idiopathic roseola (*roseola idiopathica*), frequently seen in infants and which appears in summer (*roseola aestivalis*) or autumn (*roseola autumnalis*). Later, the Austrian dermatologist I. Neumann (1832–1906), distinguished four species of roseola – "typhoid roseola", "syphilitic roseola", "choleric roseola" and "rheumatic roseola", the last species being characterized by small blotches, predominantly around the small joints, with swelling of the articulations (Neumann, 1880). The description of the disease given by Dr. Lúcio Augusto da Silva is thus compatible with the definition of the symptomatic roseola of Alibert (e.g. dengue fever is the expression or the result of distinct eruptive diseases) and of the rheumatic roseola of Neumann (e.g. the rash is accompanied by pains and swelling of the articulations).

The overall clinical picture of the Macau epidemic fever given by Dr. Lúcio Augusto da Silva is for the most part compatible with the characteristics of dengue and dengue-like outbreaks reported in the past by medical observers, concerning, in particular, the sudden onset of the disease and its great expansion in the population; the existence of well-marked stages in the disease; the biphasic pyrexia and the short duration of the fever; the existence of two cutaneous eruptions of variable character; the extension and severity of arthritic, muscular and/or bone pains and their variable duration during the convalescence; and, finally, the overall benignity of the disease. The variations observed in several symptoms (variable severity of fever or pains, lack of specificity of the second rash, etc.) and the fact that the dengue-like illness struck Macau at the same time as outbreaks of measles and roseola may account for the variety of diagnoses made by local physicians and the difficulty they had in establishing a differential diagnosis. Because the etiology of dengue fever was still unknown at the end of the 19th century, Dr. Lúcio Augusto da Silva did not bring any information

⁸ Interestingly, later medical observers reported on the inefficiency of quinine in the treatment of dengue fever: see, for instance, Dunkley (1872), Leichtenstern (1905), and Pirot (1927).

about the mosquitoes prevailing in the Portuguese colony which could have served as vectors of the dengue virus. The high frequency of the *Stegomyia fasciata* (present-day *A. aegypti*) in the locality was mentioned some 30 years later by another physician in his work on the public health of the Portuguese colony (see de Moraes Palha, 1917). Recent studies on dengue have also emphasized the high prevalence of the *A. albopictus* in Macau (Almeida et al., 2005).

The overall clinical picture of the epidemic fever that broke out in Macau in 1874 is thus compatible with classical dengue fever as it is defined today. It must be stressed, however, that the persistence of arthritic and muscular pains for weeks or months – especially in the small swollen joints or in the articulations of the inferior limbs, reported by Dr. Lúcio Augusto da Silva, the fact that both dengue and Chikungunya viruses are transmitted by the same vectors in Asia (*A. aegypti* and *A. albopictus*) and the results of phylogenetic studies which seem to date the introduction of Chikungunya virus in Asia at any time within the period ranging from 50 to 430 years ago (according to Powers et al., 2000) may also account for a CHIK etiology of the epidemic febrile disease or, at least, for the concurrent circulation of Chikungunya and dengue viruses in Macau. Simultaneous co-infection with both viruses and/or concomitant outbreaks of DF and CHIK have been documented in Asia since the isolation of the Chikungunya virus in 1953 (see, for example, Halstead, 1966; Myers and Carey, 1967; Carey, 1971; Nimmanitya et al., 1969; Nayar et al., 2007).

To conclude, this paper illustrates the great confusion that has reigned in the past over the definition and clinical characterization of dengue. The difficulty to establish a differential diagnosis is still a present-day question: clinical diagnosis must be confirmed through specialized laboratory tests and, recently, the World Health Organization has established another classification and clinical characterization of dengue infections – to encompass unusual clinical manifestations and varying grading of severity, which could serve as guide for diagnosis, disease surveillance and monitoring of patient care (see WHO, 2009a, 2011).

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