The 1932 Macau epidemic of cerebrospinal meningitis: A historical perspective and critical review of the data

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1. Introduction

In 1932 a serious epidemic of cerebrospinal meningitis, lasting no more than 3 months, broke out in the Portuguese colony of Macau, South China. Four hundred and ninety one Chinese inhabitants of Macau and the suburbs were hospitalized in the Isolation Block, opened specifically to deal with the emergency. The outbreak of this disease was considered sufficiently unusual in Macau to justify the publication of a special report by the Portuguese physician in charge of the control program of the epidemic. This article is a critical discussion of the epidemic outbreak that struck Macau in 1932. Here, we present a brief description of the disease epidemiology, followed by a review of the characteristics of epidemic meningitis that can be drawn from historical sources. Then, we draw our conclusions on the specific characteristics of this epidemic in the Portuguese colony.

2. Epidemiology of cerebrospinal meningitis

Meningitis is an acute inflammation of the meninges that may be caused by bacteria, viruses, or fungi. One particularly severe epidemic form of the disease, cerebrospinal meningitis, is caused by Neisseria meningitidis, a bacterial pathogen. This meningococcus was first isolated in 1887 from the cerebrospinal fluid of six patients presenting symptoms of meningitis, by the Austrian bacteriologist and pathologist Anton Weichselbaum who, thus, established the link between the bacterium and the epidemic form of meningitis (Weichselbaum, 1887; cited by Janssens, 1997; de Souza and Seguro, 2008). Fourteen serogroups depending on the nature of the polysaccharide capsule of the bacteria were subsequently identified, amongst which the most prevalent are serogroups A, B, C, W135, and Y. The epidemiology of meningococcal meningitis varies according to the serogroups involved and/or the regions or countries affected. In the past, serogroup A was recognized as the cause of global epidemics. However, it is now considered to be rare in Europe and North America, although it is still common in China, India, Nepal and Africa where it has caused severe epidemics during the twentieth century. Serogroups B, C and Y are currently the main cause of the disease in the United States, whereas serogroups B and C predominate in Canada and Western Europe. B, C, and Y serogroups are primarily the cause of isolated cases and/or sporadic small epidemic outbreaks (Steinhoff, 2007).

Humans are the only known natural host for the meningococcus. The bacteria are transmitted from person to person by airborne infected droplets or contact with saliva. After infecting the nasopharynx, they spread to the meninges via the bloodstream. Close and prolonged contact facilitates the transmission and spread of the bacteria between individuals. As established by
Kiefer in 1896 and by Albrecht and Ghon in 1901, the source of infection may be either clinically infected patients or clinically unapparent carriers (Kiefer, 1896; Albrecht and Ghon, 1901; Hedrich, 1931; Janssens, 1997; Steinhoff, 2007). It has been estimated that *N. meningitidis* colonizes the nasopharynx of up to 20% of adults although only a relatively small proportion will develop invasive disease depending on the virulence of the organism and/or individual host susceptibility. However, during epidemics, the proportion of asymptomatic carriers may reach as high as 95%, particularly during epidemics caused by serogroup A meningococci. In 1908, Bruns and Hohn established a positive correlation between asymptomatic carriage and meningococcal disease incidence (Bruns and Hohn, 1908; cited by Hedrich, 1931; Apicella, 2005). A similar correlation was also recorded during World War I by Glover, who reported the maximization effect of human crowding on carriage rates of meningococcal A serotype in the British Army military barracks (Glover, 1918; cited by Hedrich, 1931; Steinhoff, 2007). Upper respiratory tract infections and exposure to tobacco or wood-fire smoke have also been associated with increased meningococcal carriage and disease (Janssens, 1997; Apicella, 2005; Steinhoff, 2007). Additional studies have revealed that the disease has two peaks: the first occurring during early childhood and the second between 15 and 20 years old, with predominance among students, presumably because of the promiscuous conditions in which they live. In the past, meningococcal infection has also been frequently reported in military recruitment camps and other self-contained institutions such as jails, boarding schools, orphanages and, in earlier times, workhouses (see, for example, Lévy, 1849; Hirsch, 1886).

Meningococcal infection typically induces a wide range of symptoms, some of which are not specific, such as severe headache, fever, malaise, upper respiratory tract symptoms, weakness, nausea and/or vomiting, and signs of meningeal irritation (stiff neck, positive Kernig’s sign, opisthotonus, etc.). However, one distinguishing feature of meningococcal meningitis is the manifestation of scattered skin petechiae that may evolve as a diffuse petechial rash and in severe cases as necrotic purpura. In these severe cases, the patient may present signs of cerebral dysfunction such as stupor, delirium, impaired consciousness that, if left untreated, may progress to coma and fatal outcome. In about up to 20% of the disease cases, infection by meningococci may cause a septicemia without meningitis that is characterized by irreguler pulse, hypotension, cyanosis of extremities, shock, and visceral disorders, including abdominal pain, diarrhoea and vomiting. Differential diagnosis should be made with other kinds of purulent meningitis, tuberculous meningitis, viral meningitis and septicemia. Presently, mortality rates of treated cerebrospinal menigitis range between 3 and 5% of the cases but they can reach 30–40% in meningococcal septicemia. In the absence of antibacterial treatment, mortality rates may reach 80% and the survivors frequently present sequelae. During the nineteenth century epidemics mortality rates ranged from half to two-thirds of the cases.

### 3. Historical review on epidemics of meningitis worldwide

It seems likely that the first description of the epidemic form of meningitis was made in Geneva, Switzerland, by Gaspar Vieuusseux in the early nineteenth century. In his “*Mémoire sur la maladie qui a régné à Genève au printemps de 1805*” [Memoir on the disease that swept Geneva in the spring of 1805], he described a “malignant non-contagious cerebral fever” characterized by sudden prostration or collapse, intense headache, vomiting, convulsions in some cases, rapid feeble pulse, petechial eruptions and often death in a few hours and which he attributed to a “special constitution of the air”. Of those attacked, the number of which is not mentioned, 33 succumbed, the majority being infants and young children. In one family, four children were stricken and all died (Vieuusseux, 1805; cited by Rolleston, 1919; Hedrich, 1931; Bloomfield, 1956; Janssens, 1997; de Souza and Seguro, 2008). The results of the autopsies carried out by A. Matthey, which showed congested meninges and a kind of gelatinous substance covering the meningeal surface, established the identity of the disease known today as meningococcal meningitis (Matthey, 1806; cited by Bloomfield, 1956; Patterson, 1993; Janssens, 1997).

After Vieuusseux’s description of the epidemic form of meningitis, references to outbreaks of a disease with apparently similar symptoms but variously named by medical observers (“cerebrospinal fever”, “epidemic cerebrospinal fever”, “cerebral fever”, “cerebrospinal typhus”, “typhus cerebralis”, “sinking typhus”, “petechial fever”, “malignant spotted fever”, “meningitis epidemica”, “meningitis cerebro spinalis epidemica”, etc.) were frequently made on both sides of the Atlantic over the nineteenth and early twentieth century. 3 A review of medical data gives some insights on the epidemiological characteristics of the disease in the past. Firstly, clinical disease may occur in an epidemic or a sporadic form with a propensity to afflict predominantly children (up to 15 years of age), young adults (from 18 to 24 years of age), the latter especially when confined in army barracks and other institutions (workhouses, military camps, hotels, boarding schools, etc.). Also, meningitis cases were more common among the elderly. Moreover, the great majority of reported outbreaks in the past affected only young military recruits. This somewhat “fatal predilection” of the disease for the latter led some physicians to consider it, albeit misleadingly, to be a disease of the military (Lévy, 1849).

Furthermore, the relative predominance of some symptoms (e.g. gastrointestinal) during the course of the disease, their apparent similarity with those of typhus or typhoid fever (case of the rash, for example) and/or the fact that incidence rates increased widely during war periods added more to this confusion, some physicians considering the disease as an “anomaly” or “anatomical variant” of typhus (or typhoid) fever (see, for example, Tourdes, 1843; Murchison, 1862; Niemeyer, 1865; Hirsch, 1886). Actually, as it was understood later when *N. meningitidis* was isolated and identified as the causative agent of the epidemic form of meningitis, military garrisons provided ideal conditions (overwork, hardship, fatigue, malnutrition, overcrowded military barracks, poor sanitation and hygiene, etc.) for the emergence and spread of both diseases (Janssens, 1997; Steinhoff, 2007).

Secondly, before the advent of serotherapy in the beginning of the twentieth century, case-fatality rates were usually very high, between half and two-thirds of the cases. For example, 623 cases

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1. It is impossible to assert with any degree of certainty if all these denominations referred to the epidemic form of meningitis. For example, “spotted fever” was also, in the past, one of the denominations of the exanthematous typhus, hence the confusion between both diseases in historical medical records. Also, it seems likely that the denominations “petechial fever” and “spotted fever”, that emphasize the existence of a cutaneous eruption during the course of the disease, were used almost as synonyms in past medical literature. Finally, some of these denominations are still in use, although applied to other infectious diseases: for instance, “spotted fever” may refer to the tick-borne disease caused by *R. rickettsii* and known today as “Rocky Mountain spotted fever”. Another example is the name “petechial fever” which may apply to any febrile disease accompanied with petechiae such as meningococcal meningitis, the last stage of typhoid fever or epidemic typhus.

2. For a history of meningitis epidemic outbreaks over the world, see Hirsch (1886), Kelsch (1911), and Hedrich (1931).

3. In the past, the denomination “typhus fever” encompassed various diseases with somewhat similar symptoms, including the disease known today as typhoid fever. Both diseases were differentiated in 1837 by William W. Gerhard during an epidemic of typhoid fever in Philadelphia. Since then, the denomination “typhoid fever” applies exclusively to the disease caused by the bacterium *Salmonella typhi* which spreads via the faecal–oral route. Presently, western medicine recognizes three kinds of rickettsial typhus fever: epidemic typhus [transmitted by lice], scrub typhus (or *Tsutsugamushi disease*) [transmitted by trombiculid mites] and murine typhus [transmitted by fleas].
(133 deaths), 998 cases (715 deaths) and 206 cases (135 deaths) were respectively reported during the 1807 epidemic outbreak in Belfast, Galdston and Edinburgh. Other epidemic outbreaks around the world produced similar figures (see, for example, Boudin, 1850; Rolleston, 1919). However, it has to be said that mortality rates vary considerably between different epidemics and also at different periods of the same epidemic. Moreover, fulminating cases are more frequent at the beginning of the epidemic and mild cases at the end (Blackfan, 1922).

Thirdly, the duration of the epidemic outbreaks was highly variable, ranging from a few weeks to some months or even to a whole year or more. However, there was no relationship between the duration of an epidemic and the incidence rates. In the epidemic outbreaks at Toulon (1838), Versailles and Le Mans (1840) or at Berlin (1864–1864), for example, the number of cases was relatively low despite the long duration of the epidemic (some months to a whole year). In other instances, the number of cases was considerable regardless of the short outbreak period (Hirsch, 1886).

Fourthly, meningitis in its epidemic form has a marked seasonal characteristic. In temperate countries, epidemic outbreaks occurred in winter and/or early spring and receded in summer. This has been linked to the susceptibility of the meningococcus to dryness and heat and also to the fact that during cool weather people tend to live indoors and in close and prolonged contact (Lévy, 1849; Hirsch, 1886; Janssens, 1997). On the other hand, epidemics occur during the dry season in Sub-Saharan Africa known as “the cerebrospinal meningitis belt” (Lapeyssonnie, 1963; Janssens, 1997; Steinhoff, 2007).

4. The Macau meningitis epidemic outbreak of 1932

Data on the presence of meningitis in its epidemic form in China during the nineteenth century are scarce, a fact that led some western physicians to assume the relative absence of the disease in China, compared with the situation in Europe or North America (Cadbury, 1934). Some isolated deaths which might have been related to the disease were reported in Shanghai (for example, 3 deaths in 1898, 1 in 1900, 2 in 1901, 1 in 1902) as well as in other Chinese towns during the late nineteenth and early twentieth century. However, the situation changed significantly during the first three decades of the twentieth century, when the disease assumed an epidemic form: large epidemics with high mortality rates were reported in Hong Kong (1918), Shanghai (1920), Canton and Macau (1932). Small epidemics and/or sporadic cases were also recorded from time to time during the interepidemic years in the same cities (Vital Statistics, 1932; Cadbury, 1934).

The Hong Kong meningitis outbreak of 1918 heralded what can be considered the epidemic phase of the disease in South China according to historical medical records. It seems likely that English troops arriving from Malta transmitted the meningococcus to their Chinese servants who were taking care of their horses. The first case of meningitis was reported on February 9, the epidemic reaching its peak in March and beginning to recede in April until July/August. It lasted 6 months and was particularly deadly: 968 cases at the end ( Blackfan, 1922 ).

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Hong Kong Cases</th>
<th>Deaths</th>
<th>Macau Cases</th>
<th>Deaths</th>
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<td>–</td>
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<td>–</td>
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<tr>
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<td>1930</td>
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<td></td>
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<tr>
<td>1931</td>
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<td>16</td>
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<td>1932</td>
<td>207</td>
<td>122</td>
<td>491</td>
<td>290</td>
</tr>
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</table>

Source: Adapted from Cadbury (1934, p. 926). Data on the epidemic outbreaks at Hong Kong for the years 1919–1920 and 1928–1932 were furnished by Cadbury (1934). Those for the years 1921–1927, unfortunately without any indication of mortality rates, were drawn from the report of Peregrino da Costa (1932).

The origin of the disease in Macau is unclear. According to Dr. Peregrino da Costa, it was rampant in some communities of the neighbouring district of Heung-Shan, probably being introduced by Chinese who were fleeing from the North of China because of the Sino-Japanese conflict. The disease particularly affected the more densely populated and poorest quarters of the city. Approximately 600 persons out of a population of about 100,000 developed the disease, 491 of them being treated in an isolation Block and the others in the hospitals of the city or in their own houses. It is possible that some mild cases went unnoticed because either they cured themselves spontaneously or they have been confused with other diseases (Peregrino da Costa, 1932, p. 11). In any case, the contribution of the epidemic to the overall morbidity in Macau was relatively slight, when compared with that in Hong Kong. Of those isolated in the Block, 290 (including 30 patients presenting with a fulminant form of the disease who died soon after their entrance) succumbed to the disease and 201 recovered (overall mortality rate of 59%). All cases, except 10 (the exceptions being 1 case in a European and 9 cases in sons of Portuguese with Chinese), involved Chinese people. The disease was clinically documented in 503 cases. Spinal fluid collected by lumbar puncture presented as a cloudy fluid, characteristic of the meningeal reaction, in the majority of cases. In four cases, it was purulent and in one case, frankly haemorrhagic. In the majority of cases, it was collected without great pressure. In some cases, however, it was difficult to withdraw 10 cm³ of spinal fluid. According to the Portuguese physician, the variable amount of spinal fluid collected by lumbar puncture could provide information about the potential evolution and prognosis of the disease. Laboratory examination of the spinal fluid aiming to check the presence of meningococci and to analyze its white blood cell content and cytological composition was carried out during the different periods of the epidemic but not systematically, due to the lack of time and the short duration of the epidemic outbreak. The presence of meningococci was ascertained during direct examination of the spinal fluid. Nevertheless, isolation and identification of...
the prevalent serogroups of meningococci were not performed for the same reasons (Peregrino da Costa, 1932, p. 20).

4.1. Characteristics of the Macau epidemic

4.1.1. Season of occurrence and other meteorological data

The first cases were reported in February, the disease showing a peak of incidence in March, as it had been the case with the Hong Kong epidemic of 1918. The disease then began to subside until May 9, when it was declared as being ended. The outbreak was therefore shorter than previously observed in Hong Kong: whereas the epidemic in Hong Kong lasted 6 months, it lasted just less than 3 months in Macau. Interestingly, when the disease was subsiding in Macau (April 1932), an increase in the number of cases was observed in Hong Kong (110 cases) and Shanghai (22 cases), compared with the situation in both cities during the previous months (Cadbury, 1934, p. 930). Table 2 and Fig. 1 show the case incidence rates according to the equivalent months during the Hong Kong (1918) and Macau (1932) epidemics.

Macau is characterized by a temperate climate with four seasons marked. The first cases of epidemic meningitis appeared in winter (February), the peak of the disease being in spring (March and April). It is for this reason that Chinese people considered epidemic meningitis as a “disease of spring” (Peregrino da Costa, 1932, p. 17). Winter and spring in Macau are usually characterized by a cold/cool temperature and a relative high humidity. Variations in temperature had a marked influence on the incidence of cases: any sudden and pronounced drop in atmospheric temperature was followed a few days later by an increase in the number of cases. For example, a difference of 9˚ between the 28th and 29th of February was followed by an increase of 7 daily cases. Alternatively, days with a quasi-uniform temperature were characterized by a reduction of daily case numbers. The same correlation between a drop in temperature and an increased incidence was reported during the Hong Kong epidemic of 1918 (Olitsky, 1919; Cadbury, 1934). However, the hygrometric degree, the nebulosity of the atmosphere, the intensity of rainfall and/or of sunshine appear to have had little influence on the course of the epidemic unlike what seems to have occurred in Hong Kong where an increased incidence of disease cases was reported after a period characterized by a lack of sunshine (Olitsky, 1919; Peregrino da Costa, 1932; Cadbury, 1934).

4.1.2. Age and sex of patients

All age groups up to 64 years were affected by the disease. However, the maximum number of cases was reported amongst the 4–6-year, 6-month to 3-year and 7–9–year age groups and the minimum among the 31–33-year, 35–57-year and 58–61-year age groups. Few cases were reported over 40 years of age. In the Hong Kong epidemic, the peaks of the curve of incidence were from infancy to 5 years and 17.5 years of age. With regard to gender, 298 cases were reported among males and 205 among females (m/f sex ratio: 1.45). In comparison, during the epidemic outbreaks of Hong Kong (1918) and Canton (1932), the m/f sex ratios were 1.86 and 2.45, respectively (Peregrino da Costa, 1932, pp. 11–12; Cadbury, 1934, p. 931).

4.1.3. Contagiousness of the disease

In contrast with what was observed in past epidemics around the world, self-contained institutions (schools, boarding schools, military camps, workhouses, hotels, etc.) remained free from the disease. There were only a few isolated cases in schools, 2 in the Seminary and 1 in a soldier who was infected outside the military camp. Cases of “multiple contagion” were also rare: there were only 11 instances of 4 cases in the same house and one instance of 2 cases in the same building. The same is true for relatives of patients who were isolated with them in the Isolation Block: only one case of contagion was reported. The remaining cases were isolated cases (Peregrino da Costa, 1932, p. 17).

4.1.4. Clinical manifestations and forms

Various clinical forms of the disease were observed during the epidemic: typical form of acute cerebrospinal meningitis (213 cases, of which 80 were mild); rapid and severe forms of meningitis (198 cases, of which 30 were fulminant); septicemic and/or extended forms (50 cases); with complications (30 cases).

With regard to symptoms, fever was reported in the majority of cases and followed its normal evolution. However, there were some cases with complete apyrexia and others with hypothermia (36˚) which ended in their great majority in death (thus evocative of bacterial infectious shock). In some cases, the nape contracture was so pronounced that the occiput was almost touching the spinal column. Agitation or delirium was recorded in approximately 50% of patients. Some of them were extremely violent whereas others presented in a condition of apathy or semi-stupor. The last cases, which were sometimes confounded with cases of the septicemic form of the disease, were resistant to serotherapy and contributed widely to the mortality rate. Regarding cutaneous eruptions, except in one case, they were limited to labial herpes and to some cases of polymorphous erythema. The exception reported was a case of haemorrhagic meningitis with a purpuric eruption. Perturbations of the digestive system (stomach upset, and enteritis, particularly in the septicemic forms) were also noted. In the septicemic forms, some patients presented with delirium, high fever, and coma with a fatal outcome whereas others

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Table 2

<table>
<thead>
<tr>
<th>Months</th>
<th>Hong Kong (1918)</th>
<th>Macau (1932)</th>
</tr>
</thead>
<tbody>
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<td>Cases</td>
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<td>November</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>December</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from Peregrino da Costa (1932, p. 14). The series includes the 491 cases of the Isolation Block. Additional cases were treated outside the Block (in the other hospitals of the city or in own their houses).
presented with cutaneous eruptions, arthritis and a characteristic fever: daily accesses of 38–40 °C or intermittent fever simulating malarial fever at intervals of 1 or 2 days were interspersed with irregular feverish symptoms bearing the characteristics of a theraemic pioemic reaction. In each case, fever was well tolerated by the patient. Finally, among the complications, the author reported some cases of bronchopneumonia in children, pulmonary congestion and bronchitis in adults, myocarditis, endocarditis, inflammation of iris and optic neuritis, arthritis, etc. There were only one or two cases of earache and deafness (Peregrino da Costa, 1932, pp. 18–20).

4.1.5. Duration and outcome of the disease

Whilst the beginning of the epidemic was characterized by a predominance of benign forms, numerous cases of severe and septicaemic forms, with a mortality curve roughly parallel to the number of cases, occurred during the peak of the epidemic (Peregrino da Costa, 1932, p. 210). Of the 491 patients hospitalized in the Isolation Block, 290 (i.e. 59%) died, 30 of them before to receive any treatment and the other ones (261) from 1 to 42 days of treatment. For those who recovered, the duration of the disease varied from 5 to 60 days (see Table 3).

4.1.6. Methods of treatment and outcome

In 217 cases, the treatment consisted of spinal serotherapy; in the 244 other cases, spinal therapy was combined with intravenous or hypodermic injections of antimeningococcal serum. Unfortunately, the report does not specify the distribution of treatments according to the different clinical presentations. We just know that the choice of the method varied according to the clinical criteria of the physicians and the indications of each case. Nevertheless, the combined method was systematically used in severe cases presenting with delirium, at the initial phase of septicaemic forms bearing a heavy prognosis and in patients in a coma. In all these cases, it was of marked benefit according to Dr. Peregrino da Costa.

In the absence of any knowledge of the species of meningococci prevalent during the epidemic, all cases were treated with the polyvalent sera available during the different periods of the outbreak. The sera were acquired from various sources: the Bacteriological Institute of Hong Kong, Pasteur Institute at Bandoeng (Java) and Mulford, Hoechst, Behring and Schering commercial laboratories. All sera had some beneficial influence on the course of the disease, depending obviously upon the clinical forms in which they were used, but a great percentage of cures obtained at the beginning of the epidemic outbreak were due to the sera of the Bacteriological Institute of Hong Kong and Mulford (Peregrino da Costa, 1932, p. 23). The report does not furnish any more information about the nature of the serum and its potency with regard to its provenance and the clinical cases in which they were used. According to contemporary sources, the polyvalent serum which was used at this period was prepared from the serum obtained from horses immunized with a mixture of meningococcus strains acquired from cases of meningococcus meningitis. Wadsworth (1921) described the technique of the preparation of the serum as following: cultures of meningococci strains “were grown on serum dextrose agar slants for 17–19 h at 37 °C and were suspended in 0.85% salt solution. The inoculations were made intravenously without delay. At the beginning of immunization the first dose was a fraction of a single culture. When a large number of strains were used new strains were added as fast as possible, until 20 were injected daily. Two inoculations were made on each day, 1 h apart, with ten cultures for each inoculation. This was done to decrease the severity of the reaction. The doses were given on 3 successive days followed by a week of rest, after which another series was begun. The cultures and the method of injection were chosen so that the whole series of stock cultures was injected as often as possible. The increase of dosage was dependent upon the temperature reaction after inoculation, the aim being to secure a rise in temperature to 104 or 105 F. 5 h after inoculation, followed by a fall to normal the next morning. Trial or complete bleedings were made on the 6th day after every other series of injections” (Wadsworth, 1921, pp. 108–109).

In the case of the Macau epidemic outbreak, the dose of the serum administered at each spinal injection varied from 10 to 40 cm³, depending on the patient’s age and clinical condition, the provenance of the serum and, in some cases, the amount of spinal fluid withdrawn. Three rules were observed: firstly, a great quantity of spinal fluid was withdrawn before each injection (20–30 cm³ before the first one but less before the others) with the aim of eliminating the germs and toxic products but also of relieving congestion in the brain and preparing the meninges to a more efficient action of the serum. Actually, according to the Portuguese physician, an insufficient amount of spinal fluid withdrawn followed by a rapid injection of the serum may produce a severe phenomenon of chock because of the inhibition of bulbar centres which conduces to death immediately or a few hours later. Secondly, the serum must be injected slowly and the spinal serotherapy conducted according to the patient’s condition, the persistency of given symptoms, the presence of meningococci in the spinal fluid, etc., and not on the thermic reactions and/or the physical characteristics of the fluid. Thirdly, each new spinal injection should be realized at intervals of 6 or more days and after the desensitizing of the patient in order to prevent an anaphylactic shock which is more severe than the shock produced by intravenous or hypodermic therapy. These three conditions were essential for a good result of spinal therapy according to the Portuguese physician. Finally, the dose administered via intravenous or hypodermic injection varied from 10 to 20 cm³. During the epidemic outbreak, 2751 doses of antimeningococcal serum were administered (Peregrino da Costa, 1932, pp. 23–24).

The advantages of the mixed serotherapy, compared with spinal serotherapy alone, included a higher percentage of recoveries...
(respectively, 161, i.e. 65.98% vs. 40, i.e. 18.43%), prevention of cerebral (and other) localizations and contribution to the reduction of toxic phenomena. Despite the fact that it is not known precisely if the groups treated by each method were otherwise comparable, it should be noted – as reported above – that the combined method seems to have been used in the most severe forms (delirium, septicemia, coma, etc.) suggesting that the treatment of the general, disseminated infection by hypodermic or intravenous serotherapy was associated with a great medical benefit, compared with intrathecal serotherapy alone. Side effects of the treatment included anaphylactic reactions (chills, attack of hives, etc.) in those who received hypodermic serotherapy. Severe reactions linked to spinal serotherapy were also recorded, some leading to death in a matter of hours: fainting fit, pulse and/or irregularity of the respiration, congestion of the face, convulsions, etc. Cases of serious meningitis (characterized by violent headache, severe Kernig’s sign, high fever, congestion of the face, Cheyne-Stockes respiration type, etc.) leading to death immediately after the injection or a few hours later have also been reported (Peregrino da Costa, 1932, pp. 22–24).

5. Conclusion

The characteristics of the Macau meningitis epidemic outbreak withdrawn from the report of Dr. Peregrino da Costa are for the most part in consonance with the characteristics of epidemic outbreaks reported in the past by medical observers concerning, in particular, the seasonal preference of the disease (occurrence in winter/early spring, receding in summer), its propensity to affect predominantly small infants and children (the majority of cases being in the 4–6-year, 6-month to 3-year and 7–9-year age groups in Macau) and/or the high case-fatality rates (59%). It is possible that the mortality rate observed in patients treated with serotherapy (and more specifically by intrathecal treatment alone) is linked to the variable potency and adequacy of the serum according to the meningococci strains prevalent during the epidemic and, perhaps also, to the delay in seeking treatment. However, there were two important differences: firstly, virtually no disease case was reported amongst people living under crowded conditions (hotels, schools, boarding schools, military camps, etc.) and secondly, there were only a few cases of multiple contagion, a fact that can probably be linked to the patients’ isolation and other preventive measures taken by the physician. As reported by Dr. Peregrino da Costa, it was the first time in the history of health services in Macau that western physicians succeeded in isolating without any imposition or penalty such a great number of Chinese, a population usually refractory to western medicine. He explained this as being due to the material facilities conceded to patients (free transport to the hospital, admission without any formality, free hospitalization, possibility for the patient to be accompanied by a relative, free food for the latter, propaganda made by cured patients on the efficacy of serotherapy, etc.) (Peregrino da Costa, 1932, p. 25).

On the other hand, it has to be said that some of the epidemiological data raise questions about the precise aetiology of the epidemic disease. The evidences that strongly suggest a meningococcal aetiology include the seasonal peak, a number of highly evocative clinical presentations, the presence of meningococci in the spinal fluid, the modification of outcome by serotherapy protocol and the high mortality rates. The relatively “mild” contagiousness of the disease (“only” 600 cases were reported in a population estimated at approximately 100,000 inhabitants) is also compatible with the meningococcal aetiology for the epidemic disease. There were probably a high number of asymptomatic carriers but only few of them developed the disease. However, the small number of disease cases may also, in part, be related to the preventive measures taken immediately by Dr. Peregrino da Costa after the appearance of the first disease cases in the city. These included in particular: the removing without delay of the patients in the Isolation Block; the disinfection of hotels, schools, cinemas and/or other places frequented by infected patients; the disinfection of the houses of suspected or confirmed cases; the disinfection of the clothes of the patient and of the relative isolated with him; the installation in different places of the city, including in the hospitals, of free posts for disinfection of the throat and nasal passages and the compulsory disinfection of the throat and nasal passages of the patients’ relatives. The report does not give any precision on this last measure. However, an official note of the health services of Macau (Nota no. 143 dated of 22/02/1918) aiming to prevent the invasion of the city by the meningitis which was raging in Hong Kong in 1918 brings some information on the purpose of this last measure and on the nature of the antiseptic substances used for this end. The disinfection of the throat and nasal passages has the purpose to prevent upper respiratory tract infections and to kill the meningococci present in the nasopharynx as it is known that meningococci colonize the nasopharynx of healthy persons (carriers) whose important role in the dissemination of the disease has been established by earlier medical observers. Mouth washes and gargles and/or spraying the throat with antiseptic substances with the purpose of cleaning the mouth and throat and also nasal aspirations were the methods indicated at this period. Different antiseptic substances were employed for this end: gargles with a solution composed of potassium chloride (3%), borax (4%) or thimol (1/4000); nasal aspirations of boric acid (10%) powder; distillation into the nostrils of menthol, boric acid or Vaseline balm, etc.5

Whereas the characteristics of the epidemic meningitis in Macau we have listed above are in favor of the meningococcal aetiology, other characteristics of the disease tend to point towards a viral origin, in particular the low number of petechial forms and the high number of benign forms (80 of the 213 reported cases of acute cerebrospinal meningitis). Unfortunately, in the absence of haemoculture, it is difficult to decide whether or not these benign forms were due to the meningococci.

In conclusion, this review of the medical literature underlines our poor understanding of the global epidemiology of meningococcal infection, and in particular the specific determinants for endemic/sporadic/epidemic patterns of the disease. However, it reinforces the idea that these patterns evolved over time and that meningococcal infection appeared in different periods and different geographical locations as a typical emerging or re-emerging disease, presumably in relation to the introduction in specific niches of previously unknown bacterial serotypes and/or with modification of social behaviour.

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5 Nota no. 143 de 22-2-1918 da Repartição do Serviço de Saúde de Macau. See also Blackfan (1922) for a review of the main antiseptic substances used in the past in the prophylaxis of the carriers of the disease.
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