1
Historical Aspects

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1.1
The Origins of Meningococcal Disease

The story of meningococcal disease has mirrored the scientific and technological developments of the time. Each advance, from early microscopy through bacterial culture and classification techniques to mathematical modelling, genetics, molecular microbiology and proteomics, has been reflected in advances in our understanding of, and latterly, control of meningococcal disease.

For most of the 19th century, communications between scientists were limited and the disciplines of microbiology and epidemiology did not exist. Medicine was primarily observational, much more art than science, and there were few rational, science-based treatments. Without diagnostic tools, it was impossible to differentiate one "spotted fever" from another. In this pre-technological time, it would have been very difficult to differentiate sporadic cases (or even outbreaks) of meningococcal disease from conditions such as typhus, typhoid and smallpox. Thus it is very hard to say whether Vieusseux really was the first to describe an outbreak of meningococcal disease when he documented 33 deaths from a "spotted fever" accompanied in most cases by meningitis in Eaux-Vives, a small suburb of Geneva, Switzerland.

Nevertheless, some early clinicians were capable diagnosticians and the signs and symptoms of meningococcal disease – at least in the form in which we see it today – are in many ways strikingly characteristic, especially in its epidemic form. Could it truly have been a new disease in 1805? This must remain a possibility. We know now that the meningococcus, as well as being highly adapted to the human nasopharynx (suggesting a long and intimate commensal relationship with Man), is also a highly transformable bacterium, capable of acquiring and integrating DNA from a range of microbes with which it comes into contact. It remains a possibility (that cannot be proved or disproved) that, in a small Swiss community in 1805, a nasopharyngeal commensal neisseria acquired by chance the genetic material that allowed it to become the meningococcus we know today.

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1.2 The 19th Century

Epidemiology: Outbreaks and Epidemic Periods with High Case Fatality Rate

For most of the 19th century, meningococcal disease was recognized and described principally when clusters of cases occurred. Many were associated with the military. In this pre-antibiotic era, the disease was associated with very high mortality (70% or more), though not all died swiftly. There are numerous accounts of patients whose rash and fever settled over a week or so, leaving the afflicted individual comatose, lingering for days or even weeks before finally perishing. Presumably in such cases, patients survived long enough to mount a partial or even complete immune response, but by the time the infection was controlled, brain damage was severe and the chance of survival slight. August Hirsch, a medical historian, published by far the most comprehensive account of the disease during this period in 1886.

First Isolation of the Meningococcus

It was only towards the end of the century in 1887 that Anton Weichselbaum, working in Vienna, isolated the putative bacterium causing the disease from six of eight fatal cases. A pneumococcus was isolated from the remaining two. Jaeger, a German microbiologist disputed these findings, attributing the cause of the disease to an intracellular chaining coccus (therefore presumably a streptococcus) from fatal cases in a military outbreak in Stuttgart [1]. This confusion may have arisen either because, as we know now, meningitis can be caused by a range of different microorganisms (Jaeger may have isolated a pneumococcus), or (more likely) Jaeger's cultures were contaminated. Keeping cultures pure was a major problem for early microbiologists. Before long, Weichselbaum's findings were replicated and vindicated and his "*Diplococcus intracellularis meningitidis*" was recognized as the true cause of meningococcal meningitis.

Lumbar Puncture in Living Patients

The demonstration of the practicality of lumbar puncture as an investigative procedure by Quincke in 1893 not only provided a means by which a diagnosis could be established in a significant proportion of patients, but perhaps more importantly paved the way for intrathecal serotherapy.

Isolation of Meningococci from Throat Swabs

An important advance in developing an understanding of the mechanism of spread of the disease was the first isolation of meningococci from throat swabs and its differentiation from gonococci by Kiefer in 1896. The end of the 19th century was a fertile period for traditional medical microbiology, with the isolation and characterization of a host of medically important bacteria, reflecting advances in bacterial culture techniques and in classification methods.

1.3 From 1900 to 1920

Immunotherapy

The first major advance of the new century was the development of meningococcal antisera by German and US researchers. In Germany, Jochmann and his team raised antisera in rabbits and then horses, demonstrated protection in a guinea pig model and then proceeded to human trials, beginning with subcutaneous administration and then utilizing the intrathecal route. By 1908, Flexner and Jobling in the USA were able to report 25% mortality in a large series – a dramatic improvement in outcome when compared with the death rate in untreated patients. Serum sickness and the occasional case of secondary meningitis were among the problems with this new treatment.

Epidemiology: World War I – Investigations in Recruit Training Camps

In the UK, notification of a range of infectious conditions such as cerebrospinal meningitis and typhoid was made a legal requirement for doctors in 1912, having been introduced on a piecemeal basis, city by city, since 1905.

Most combatant countries began to experience upsurges in meningococcal disease incidence with the mobilization of millions of young men into the military establishment. It was quickly recognized that the problem was largely restricted to new recruits. Attack rates were low in seasoned troops. Captain JA Glover of the British Royal Army Medical Corps (RAMC) led a major program of investigation that lasted the duration of the war at the Guards Training Depot at Caterham in south London. Key findings were an association of disease with the winter months, with periods of severe overcrowding and with large rises in the prevalence of meningococcal nasopharyngeal carriage prior to the onset of cases of disease.

Efforts were made to control the disease through interventions that included increasing the space between beds, improving the ventilation in accommodation huts, deferral of typhoid vaccination and the use of zinc sulfate spray as a nasopharyngeal disinfectant for recruit troops where there had already been a case. In retrospect, perhaps the first two of these measures were the most important. For whatever reason, by the time of the 1918–1919 influenza epidemic, the disease had been controlled and there were only two cases of cerebrospinal fever that winter in a still-overcrowded camp. Subsequent work showed that high carriage rates were not always associated with disease and that acquisition rates and the intrinsic virulence of the circulating meningococci were more important.

First Vaccine Trials

The first generation of meningococcal vaccines were crude by today's standards, comprising no more than standardized suspensions of killed meningococci. In 1912, Sophian and Black in the USA used a heat-killed vaccine to immunize first a group of medical students and then larger groups of family case contacts and nurses. Side-effects were similar to those of the newly developed typhoid vaccines. (In view of the likely endotoxin content, a red, swollen and sore arm at the injection site must have been almost universal!)

Greenwood used a similar, but polyvalent vaccine during a large outbreak of disease in and around Salisbury, England, in 1915. Two doses of the vaccine were given to more than 4000 individuals of whom approximately 25% were schoolchildren. Over the next year, there were seven cases among just over 5000 unvaccinated children and no cases in the vaccinated children. The difference in disease attack rates was not significant.

In a US military camp outbreak in 1917, a whole-cell vaccine was given to 4700 soldiers of a total population of 25 000 [2]. After a 5-month follow-up period, there were 43 cases amongst unimmunized troops, compared with a single case in a fully vaccinated recruit and two cases in partially immunized soldiers, giving a short-term efficacy of 87%.

Meningococcal Typing

Gordon and Murray, RAMC microbiologists, raised antisera to meningococci in rabbits and used these to develop a typing system (types I–IV). A French typing system developed a few years later at the Pasteur Institute, Paris, utilized letters rather than numerals (A–D). It took until 1950 for an international committee to unify the two schemes to create the serogroup classification that remains in use today (Table 1.1). All major outbreaks that occurred between 1914 and 1945 were caused by strains that would now be designated as serogroup A.

Table 1.1 Relationships between historical and present-day classifications of meningococcal serogroups.

Reference	Year	Classification
Gordon, Murray [3]	1915	I II III IV
Nicolle, Debains, Jouan [4]	1918	A B A B C D
Recommended (Int. Assoc. Microbiol.)	1950	A B A D C

1.4
From 1921 to 1939

Epidemiology

There were a number of notable outbreaks of meningococcal infection on both sides of the Atlantic during the late 1920s, caused by serogroup A strains. Major serogroup A epidemics occurred in the sub-Saharan region of Africa, the Meningitis Belt, but were poorly documented.

The Meningococcal Capsule

In the US, Geoffrey Rake and his colleagues carried out detailed carriage studies and characterized the nature of the meningococcal capsule. His group showed that "smooth" meningococci were well capsulated and could be agglutinated by specific anticapsular antisera, in contrast to "rough" strains. Freshly isolated meningococci were more likely to be "smooth", i.e. to express abundant capsular material. He and his colleagues went on to demonstrate that the meningococcal capsule was composed of polysaccharide. This work was published in 1935 and it seems inevitable that it would have led to the development of purified capsular polysaccharide vaccines but for the waning of interest (and probably funding) with the discovery of the dramatic therapeutic potential of sulfonamides.

Sulfonamides – The First Specific Therapeutic Agents

Following tests in animals, sulfanilamide (Prontosil), the first sulfa drug used therapeutically, was reported in 1937 to be highly effective in human meningococcal infections. It was followed almost immediately by reports of the use of sulfapyridine – better known as M&B 693 (May & Baker). Not surprisingly, sulfonamide treatment immediately gained widespread acceptance, not only for meningococcal meningitis but also for pneumonia and a whole range of other infections. Sulfonamides formed the mainstay of meningococcal disease treatment throughout World War II.

1.5
From World War II to 1960 – Epidemiology

At the outbreak of World War II, there were again major outbreaks of meningococcal disease in combatant countries. In the UK there were more than 12 000 cases in 1940 and the USA also experienced a major upsurge in disease a little later with a peak of over 18 000 cases. In both countries, though there was a strong association with the military, there were also high rates of disease in civilian populations. Fortunately, sulfonamides and then later penicillin were widely available to treat affected patients. In the UK, case fatality rates dropped to below 20% (and were probably lower than this "headline" figure due to relative under-ascertainment of surviving cases).

With the availability of an increasing range of potent antibiotics in the years after World War II, it must have seemed that meningococcal disease had been defeated. Across the developed world rates of disease were generally low, although major epidemics continued to occur in the Meningitis Belt countries.

In 1950, the International Association of Microbiologists rationalized the classification system for meningococci, opting for the French nomenclature that had been in use since 1918.

During the 1950s, there was a gradual change in the disease epidemiology in many developed countries, with the decline of serogroup A strains and their replacement by a more diverse range of meningococci within which serogroup B strains generally predominated, with serogroup C also present.

Though numbers of cases in most European countries and in the USA remained at levels that were relatively low by historical comparison, case fatality rates remained stubbornly in the region of 15% or so and there was a better understanding of the appreciable morbidity amongst survivors. Meningococcal septicemia was recognized to be associated with very high case fatality rates.

1.6 From 1961 to 2005

Epidemiology

There was a timely reminder in 1963 that meningococcal disease continued to pose a major public health problem when Lapeysonnie documented the major epidemics of the disease that had been occurring (and continued to occur) in the Meningitis Belt. Lapeysonnie characterized the area in geographical terms, extending from northern Nigeria and Upper Volta in the west to Somalia in the east, i.e. stretching right across the continent. Epidemics continued to occur throughout the period with attack rates sometimes briefly in excess of 500 per 10^5 population.

In the 1980s and 1990s, the incidence of meningococcal disease began to rise again in many countries. Outbreaks of serogroup B disease were documented in Cuba, Brazil, Chile, Norway, the United Kingdom and New Zealand, among other countries. In the 1990s, many European countries, including Spain, the Czech Republic and the United Kingdom, saw increases in the incidence of serogroup C disease caused by a strain of very high virulence. The start of the new millennium was marked by the occurrence of outbreaks of W-135 disease amongst Hajji pilgrims visiting Mecca. The responsible strain belonged to the same clone as that causing the recent serogroup C disease in Europe, suggesting that the clone had acquired a new capsule gene [51].

Meningococcal Typing

Typing of meningococci rose to a fine art with phenotypic characterization reflecting variations in capsular polysaccharide, class I and II/III (porA and porB) outer membrane proteins, lipooligosaccharide moieties and resistance to sulfonamides. Multilocus enzyme electrophoresis (MLEE), a surrogate for a genetic typing system, was used widely for investigation of outbreaks and for characterization of strain collections. In 1998, the development of multilocus sequence typing (MLST) provided a reproducible and unambiguous means of genetically characterizing meningococci. With rapid development of the world wide web, data on meningococcal sequence types are now held on an open-ended, open-access database, available to researchers throughout the world.

Vaccines

Despite many different approaches, the year 2005 was reached without the availability of a universal serogroup B vaccine suitable for most developed countries. Though outer membrane vesicle serogroup B vaccines tailored to specific strains had been made in Cuba and Norway, they proved unsuitable for widespread application. The publication of the sequence of the men B genome by a group led by Rino Rappuoli of the Chiron Corporation lifted hopes that a number of potential vaccine candidate antigens would be identified, but this hope has yet to be translated into reality. Many other approaches to the development of serogroup B vaccines are currently being explored.

There has been more better progress in the control of disease caused by strains of serogroups A and C. Conjugated polysaccharide vaccines have been developed for both of these serogroups, and in the case of the latter, deployed with tremendous success, first in the United Kingdom and then more widely in many European countries. Early in the new millennium, and in a politico-economic development of enormous importance, the Microsoft Corporation founder, Bill Gates, donated many tens of millions of dollars to a program aimed at developing and rolling out conjugated vaccines in the countries of the Meningitis Belt. Serogroup A conjugates are now being manufactured in India at low cost; and the groundwork is being laid for their use in Africa in the next few years.

Clinical Management

With an increasing appreciation of the importance of the host response to meningococcal infection as a factor in tissue damage and poor outcome, there have been a number of new therapeutic modalities developed that aim to block some of the damaging host immune responses that characterize severe meningococcal sepsis. As yet, none has been shown to impact significantly on outcome.

On a more practical note, there has been a dramatic reduction in the meningococcal disease case fatality rate during the past 10–15 years as a consequence

Table 1.2 Milestones in the history of meningococcal disease.

Year	Author(s)	Milestone
Classical	Hippocrates, etc.	Description of headache with fever. Uniformly fatal. Could have been any one of a number of diseases.
1684	Willis	*"A description of an epidemical feaver in 1661"*. English physician described an outbreak of a spotted fever [6]. Could have been typhus or typhoid.
1806	Vieusseux	First well documented description of an outbreak of meningococcal disease in Eaux Vives, near Geneva, Switzerland [7]. Most cases had meningitis.
1806	Danielson, Mann	First description (independent of Vieusseux) of an outbreak of meningococcal disease in the New World (Medfield, Mass., USA) [8].
19th century	Hirsch	Medical historian documented outbreaks in Europe and USA throughout the 19th century (1805–1882) [9]. Described three principal epidemic periods with very high case fatality rates.
1884	Marchiafava, Celli	Italian physicians describe oval micrococci (small round Celli bacteria) within leucocytes in spinal fluid of patients dying with meningitis. Negative cultures [10].
1887	Weichselbaum	Viennese physician isolated "*Diplococus intracellularis meningitidis*" from spinal fluid of six of eight cases of primary, sporadic meningitis. First isolation of a meningococcus [11].
1893	Quincke	German physician carries out first lumbar puncture in a living patient [12].
1894	Voelcker	First report of supra-renal apoplexy (later known as Waterhouse-Friderichsen syndrome) [13].
1896	Heubner	German microbiologist isolated meningococci from spinal fluid of living patient [14].
1896	Kiefer	German microbiologist isolates meningococci from the throat (nasopharyngeal carriage) [15]. Differentiated meningococci from gonococci.
1906	Jochmann	German physician raises animal antisera, tests in animals and attempts intrathecal serotherapy [16]. First rational treatment.
1908	Flexner, Jobling	Extensive use of horse antimeningococcal sera for intrathecal treatment in both USA and Germany [17]. Case fatality rate halved in treated patients (still only a small minority).
1911	Netter, Debré	Updated Hirsch's account of outbreaks [18].
1911	Waterhouse	English physician also described supra-renal apoplexy (but could have been hemorrhagic smallpox) [19].

Table 1.2 (continued)

Year	Author(s)	Milestone
1912		Introduction of a national system of infectious disease notification (including cerebrospinal fever) in the UK.
1912	Sophian, Black	First whole-cell vaccine tested in USA [20].
1914–1918		Major rise in incidence of meningococcal disease in WWI combatant countries.
1915–1916	Greenwood	First whole-cell vaccine deployed during outbreak in Southern England. Attempt at evaluation of efficacy unsuccessful [21].
1915	Gordon, Murray	English army microbiologists developed first serological classification system [3].
1914–1918	Glover	Detailed epidemiological studies in army recruit depots in England linking overcrowding and high rates of carriage with disease [22].
1918	Friderichsen	Also described supra-renal apoplexy (now Waterhouse-Friderichsen syndrome) [23]. The most mis-spelt eponym in the history of meningococcal disease!
1918	Nicolle	Pasteur Institute microbiologists published a new serological classification [4].
1919	Rolleston	Detailed review of meningococcal disease during WWI. Association with respiratory viral infections and influenza recognized [24].
1920s–1930s		Outbreaks of disease in urban communities in Europe and USA. Recognition of major outbreaks in sub-Saharan Africa.
1929	Fleming	Discovered penicillin. Subsequently developed by Florey, Chain, et al. [25].
1933	Rake, Scherp	US microbiologist described rough and smooth (i.e. encapsulated) strains. Subsequently showed that capsule was composed of polysaccharide [26]. Paved the way for development of capsular polysaccharide vaccines.
1937	Schwentker	"*Treatment of meningococcic meningitis with sulfanilamide*" [27]. A major landmark. The first specific and highly effective treatment.
1939	Banks et al.	Use of sulfonamides for treatment becomes widespread and remains so until end of war [28, 29].
1940	Fairbrother	Sulfonamides found to clear nasopharyngeal carriage making chemopropylaxis possible [30].
1940s		Major epidemics of meningococcal disease in combatant countries in WWII.
1950	Intl Assoc. Microbiol.	New meningococcal serogroup nomenclature (A, B, C, etc.), still in use today.
1956	Branham	Canadian microbiologist wrote detailed review of the history of meningococcal infection [31].

Table 1.2 (continued)

Year	Author(s)	Milestone
1963	Lapeysonnie	Documented massive epidemics of meningococcal disease in sub-Saharan Africa from 1940s [32].
1963	Millar	Emergence of sulfonamide resistance [33]. Hampered chemoprophylaxis and sparked vaccine development program in US military.
1969	Hollis	Identification and characterization of *Neisseria lactamica*. Permitted distinction between meningococcus and lactamica in carriage studies [34].
1969	Gotschlich et al.	Major US military research program results in the publication of seminal papers on meningococcal capsular polysaccharides, mechanisms of immunity to infection and the development and testing of the first polysaccharide vaccines [35–39].
1982	DeVoe	Detailed review of understanding of meningococcal disease pathogenesis [40].
1987	Achtman	Electrophoretic typing (MLEE); first genetically based classification system allowing a better understanding of meningococcal evolution [41].
1988	Botha	First report of a penicillinase-producing meningococcus [42].
1991	Sierra	Cuban microbiologists developed strain-specific outer membrane vesicle vaccine for local outbreak of serogroup B disease [43]. Outbreak declined.
1990s	Various	Limitations of plain polysaccharide vaccines appreciated. Technological development of conjugated vaccines.
1991	Kristiansen	First report of PCR test for diagnosis [44].
1995	Cartwright	Updated history of the disease [5].
1997	Levin et al.	Human gene polymorphisms linked to risk of disease [45, 46].
1998	Maiden	Multi-locus sequence typing (MLST) of bacteria [47]. Open-access electronic sequence type database created.
1990s	Levine	Improved clinical management reduced case fatality rate [48].
1999	Miller et al.	Introduction of conjugated serogroup C vaccine in the UK. Men C disease rapidly controlled [49].
1999	Chippaux et al.	Men A + C conjugates enter clinical trials in Africa [50].
2000–2001	Taha	Outbreaks of W-135 disease in Hajji pilgrims [51].
2000	Rappuoli et al.	Men B genome sequenced [52]. Candidates for serogroup B vaccines identified [53].

Table 1.2 (continued)

Year	Author(s)	Milestone
2001	Gates	Computer billionaire funds Meningitis Vaccine Project – a major program of meningococcal vaccination in sub-Saharan Africa. Politics and economics meet microbiology and epidemiology!
2005		Efforts to develop safe and effective men B vaccines continue.

of: (a) familiarity with the symptoms of the disease amongst parents, teenagers and health care professionals leading to earlier recognition and treatment, (b) a better appreciation that time is precious in early management if the disease process is to be arrested – the concept of the "Golden Hour" and (c) the development and widespread implementation of good protocols for case management, leading to a more consistent standard of treatment with fewer mistakes in fewer hospitals. These simple measures have led to a reduction of more than 50% in the case fatality rate in the United Kingdom.

In 2005, meningococcal resistance to penicillin remains no more than a very occasional curiosity. One hopes that it may remain so, at least until we are able to control meningococcal disease through vaccination.

1.7 Conclusion

This is a necessarily brief account of only some of the milestones in the history of meningococcal disease. These are set out in Table 1.2 for ease of reference. Readers wishing for a little more detail are referred to the first chapter in "Meningococcal Disease", a book that I edited in 1995 [5]. Since this book is now out of print, copies of the chapter and a more extended historical bibliography can be obtained directly from the author (Prof. Keith Cartwright, Brobury House, Brobury, Herefordshire, HR3 6BS, United Kingdom).

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