Lumleian Lectures

ON

CEREBRO-SPINAL FEVER

SIR HUMPHRY ROLLESTON

With the Author's Compliments

W. D. R

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CEREBRO-SPINAL FEVER

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BY

SIR HUMPHRY ROLLESTON, K.C.B.,

M.D., F.R.C.P.

EMERITUS PHYSICIAN, ST. GEORGE'S HOSPITAL; PRESIDENT OF THE ROYAL SOCIETY OF MEDICINE; TEMPORARY SURGEON-REAR-ADMIRAL, R.N.

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ON

CEREBRO-SPINAL FEVER.

LECTURE I.

Introduction.

Mr. President, Censors, and Fellows of the College,—For the honour of entrusting me with the delivery of the Lumleian lectures for 1919 I desire to express my grateful thanks.

In 1581 Dr. Richard Caldwall, sometime senior student of Christ Church and President of this College in 1570, and John, Baron Lumley (1534–1609) founded a surgical lecture which was subsequently altered in the terms of the appointment and scope. It would appear probable that Caldwall was responsible for the original lines on which the lectureship was founded, as his only extant work is a translation of the "Tables of Surgerie," by Horatius Morus, a Florentine physician. Times have indeed changed since this lectureship was started; 300 years ago William Harvey had recently (1615) begun his 41 years' tenure of office, and in 1616 had given a complete survey of the circulation.

Cerebro-spinal fever has not, so far as I can make out, previously been taken as the subject of these lectures, and as it has become prominent during the war and has been the subject of numerous observations and much investigation it is, perhaps, appropriate to take a survey of our present knowledge of the epidemiology, clinical picture, and treatment of the disease in these three lectures. I have been so fortunate as to have seen the notes and many of the cases in the Royal Navy since the outbreak of war, and have freely utilised this material.

The official nomenclature of "meningococcal infection, varieties (*a*) cerebro-spinal meningitis, (*b*) posterior basal meningitis," only dates from the last revision published in 1918; before that the heading had always been "Cerebro-spinal fever, synonym epidemic cerebro-spinal meningitis,"

the only alteration ever made being the omission of the additional synonym "malignant purpuric fever," which made its sole appearance in the first edition of 1869. In the Manual of the International List of the Causes of Death (1911) based on the second decennial revision by the International Commission at Paris in July, 1909, cerebro-spinal fever is the third subheading of simple meningitis, and is separated from posterior basal meningitis which, with a number of other meningeal diseases, is included in the first division of simple meningitis. It was perhaps a prophetic instinct that led the framers of our first nomenclature to place cerebro-spinal fever among the general rather than among the nervous diseases. For the title of these lectures, cerebro-spinal fever, though used in the same sense as, is perhaps preferable to, meningococcic infection, which might rather suggest a more considerable discussion of pathological and bacteriological problems than can properly find a place in these lectures which are now understood to be devoted to clinical medicine. By cerebro-spinal fever is meant meningococcic infection both in its general and local manifestations, meningitis being the most frequent and clinically important of the local changes.

Historical.

The first undoubted account of the disease is of an outbreak in and around Geneva in the winter of 1805 by Vieusseaux; by the next year it had spread to America and was described at Medfield, Massachusetts, by Danielson and Mann, who appear to have been ignorant of the epidemic at Geneva; and in 1806–7 the Prussian Army were attacked. In this country the first cases verified by necropsy were at Sunderland in 1830, but, as Ormerod [1] suggests, a group of cases, some with purpura, observed by Gervis [2] at Blackaton on Dartmoor in 1807 may have been of this nature. In 1827 Alexander Monro, in the course of an account of chronic hydrocephalus, described what is now known as posterior basic meningitis, but was not differentiated from tuberculous meningitis until 1878 by Gee and Barlow [3] in their paper on cervical opisthotonos in infants. In 1897 J. W. Carr [4] elaborated this distinction in his account of non-tuberculous posterior basic meningitis of infants.

As the acute disease was known as the "spotted fever" and as the "black death," confusion with other fevers of a malignant form, and especially typhus, has been inevitable, and this must be taken into consideration in connexion with any attempts to recognise descriptions of cerebro-spinal fever in the works of Hippocrates, Celsus, Paul of Ægina, and in other accounts written before 1805. Hamer [5] insists that Sydenham's description of the new fever (influenza) in 1685 portrays the clinical features of cerebro-spinal fever

in 1915. Creighton[6] remarks that some symptoms of the epidemic fever of 1771 in Ireland suggest cerebro-spinal fever; and while admitting that the clinical accounts of the old epidemics would apply equally to typhus, enteric, or cerebro-spinal fever, Councilman, Mallory and Wright[7] point out that Sir John Pringle's account (in 1750)[8] of jail fever with suppuration about the brain is compatible with the interpretation that the cases were meningococcic meningitis. Impressed with the frequency and endemicity of the disease in parts of Central Africa, where few Europeans have travelled, Chalmers and O'Farrell[9] raise the interesting question whether the real home of the disease may not be Central Africa, whence it may have passed to Egypt, and so have been conveyed by carriers among Napoleon's soldiers to France and to America; but their search among old medical and other records of the Sudan has not been rewarded by any positive evidence in favour of their suggestion.

In the absence of bacteriological help, on which the accurate recognition of cerebro-spinal fever at the present day so absolutely depends, the diagnosis is open to so many fallacies that past records afford little evidence on which to form reliable conclusions. Thus, as late as 1865 such an authority as Murchison[10] stated that "the grounds for drawing a specific distinction between epidemic cerebro-spinal meningitis, or the spotted fever of America, and typhus are most inconclusive," and argued that the cases at Dantzic described by Burdon Sanderson were really typhus. Although there can be little doubt that it was not a new disease in 1805, and that, as Hamer says, the meningococcus was not born in that year, it is difficult to say more than this.

Increase of the Disease during the War.

It is unnecessary to detail the epidemics of the disease since 1805, as Hirsch did this up to 1884, and Bruce Low[11] continued the task from 1886 to 1916. Hirsch described four periods from 1805 to 1830, from 1837 to 1850, from 1854 to 1874, and from 1876 to 1882; some writers prolong the fourth period up to the present time, but it is probably better to start the fifth period from 1903, New York suffering severely in 1904–5, Silesia in 1905–7, France in 1909–10, and Texas in 1912.

In Great Britain 1907 was marked by outbreaks in Belfast (623 cases with 135 deaths) and in Glasgow (998 cases with 715 deaths), and in Edinburgh (206 cases with 135 deaths). No considerable outbreak occurred in England and Wales until the first year of the war; in 1912, when compulsory notification was permanently brought in, there were 272 cases with 142 deaths, in 1913 there were 304 cases with 163

deaths (B. Low), and in 1914 300 cases with 206 deaths. In 1915 there were 2343 cases with 1521, or 64·9 per cent., deaths ; in 1916, 1278 cases with 838, or 65·6 per cent., deaths ; and in 1917, 1385 cases with 906, or 65·4 per cent., deaths (Reece [12]).

There is therefere no question as to the increase of the disease in this country after the outbreak of war. The cause, as will be discussed later, appears to be mainly the crowding together of young recruits in camps and barracks in conditions which, on the one hand, led to an increase in the carrier rate, and on the other, reduced the resistance of the individual. As the disease appeared on Salisbury Plain after the arrival of the first Canadian contingent, as four cases occurred in their camp at Valcartier, in Canada, in September, 1914, three on the way across, and some after their arrival, it was popularly suggested that the disease may have thus been introduced into the country. This, of course, is quite untenable, for, as has already been mentioned, the existence of the disease in this country was well recognised. But it might be argued that the advent of the Canadian contingent aggravated the spread of the disease. Thus, at Portsmouth the disease began on Jan. 15th, 1915, at Eastney Barracks, among men who came in contact with a Canadian football team visiting there on Jan. 9th ; this, however, may have been a coincidence, for the disease broke out simultaneously in other parts of the country, and none of the Canadian visitors were known to have been carriers.

The Medical Research Committee's Special Advisory Committee wrote that "the reports from the Salisbury Plain area suggest, not indeed that the Canadians imported a new disease ..... but that they did introduce a virulent strain of the meningococcus, and were in some degree responsible for its spread." Adami [13] vigorously controverts this, and points out that the strains obtained from the Canadian cases were identical with those isolated from purely British cases.

Epidemics vary much in their duration ; from days and weeks to months, but usually last for six months. Dopter quotes examples of the persistence of the disease in towns for years ; thus at Bayonne it lasted for seven years (1837–1843) and at Versailles for five years (1839–1843).

Change of Type of the Disease.

The question of the change of type of the disease acquires considerable interest from Dopter's [14] observation that in France the type of the infecting organism underwent a change during the European war ; and Netter correlated the greater frequency of septicæmic cases and lesions, such as rashes, arthritis, iridocyclitis, with this alteration of the infection from Type A (Gordon's Types I. and III.) to Type B

(Gordon's II. and IV.). This question is referred to later under the heading of meningococcic purpura without meningitis. Kennedy and Worster-Drought [15] investigated the relation of the type of meningococci to the clinical picture in 22 cases and found that 8 cases infected with Gordon's Type I. were all very gravely ill, with a fatal issue in 6 ; that of 6 cases with Type III. some were severe and some moderately severe ; and that the 8 cases of Type II. all recovered ; of Type IV. there were no cases. These few observations suggest that Types I. and III. (Nicolle Type A) are more virulent as regards the meninges and Types II. and IV. (Nicolle Type B) specially prone to cause septicæmia and extra-meningeal metastases (vide also meningococcæmia). But in a recent small outbreak of 10 cases due to Type II., which was under my observation, the meningitic manifestations were very severe, and the mortality was 60 per cent. Adshead [16] analysed 49 cases in which Gordon's types of meningococci had been determined, with the object of ascertaining if there were any conformity between the type on the one hand, and the seasonal incidence, symptoms, and mortality on the other hand, but did not feel justified in drawing any definite conclusions. Observations on a large number of cases are necessary before coming to any final conclusion on the relation of bacterial strains and clinical symptoms.

Epidemiology.

Though it naturally attracts more attention when in epidemic form, cerebro-spinal fever is really endemic and smoulders on for years, breaking out under favourable conditions into epidemics. These endemic or sporadic cases bridge over the interepidemic periods and keep the disease from dying out. It is by the suppression and isolation of such cases that the disease should be finally eradicated. At and before the commencement of epidemic outbreaks the sporadic cases become more frequent, and it may be difficult to draw the line between an increased number of sporadic cases and an epidemic. It may, indeed, be doubted if even in 1915 there was a real pandemic of cerebro-spinal fever in this country ; small outbreaks "affecting a number of persons simultaneously or within a short interval of time" (part of Greenwood's [17] definition of an epidemic) certainly occurred, but for the most part the cases continued to crop up at intervals or in couples. The special advisory committee upon bacteriological studies of cerebro-spinal fever during the epidemic of 1915,[18] adopting Dopter and Arkwright's [19] view, concluded that the epidemic is not one of cerebro-spinal fever as such, but what may be termed a "saprophytic epidemic" of the meningococcus in the throats of the population, cerebro-spinal fever being an epiphenomenon of this epidemic, due to a secondary

systemic invasion from its saprophytic focus in the naso-pharynx, occurring in spare and isolated instances which, as a rule, appear unconnected with each other.

Seasonal Incidence.

In this country the vast majority of the cases occur during the first six months of the year, the numbers falling to a low level during the summer months, thus contrasting with acute poliomyelitis, and not rising again until the end of December.

Among 3621 cases occurring in England (including London) and Wales during 1915 and 1916 Colonel R. J. Reece found that there were in the first quarter of the year 1355, or 37·4 per cent.; in the second 1444, or 39·6 per cent.; in the third 448, or 12·4 per cent.; and in the last quarter 374, or 10 per cent. Thus, in the first six months of the year 77 per cent. of the cases arose. Among the 509 cases in the Navy during the first four years of the war 298, or 58·5 per cent., arose in the first quarter; 120, or 23·5 per cent., in the second quarter; 43, or 8·4 per cent., in the third; and 48, or 9·4 per cent., in the fourth quarter of the year. Out of the total 509 cases, 353, or 69 per cent., occurred during the first four months (1915–18), and during the first half of the year 418, or 82 per cent.

The disease, however, never disappears entirely; in 1915 and 1916 cases occurred in every month of the year (Reece). The seasonal prevalence probably depends on a number of accompanying factors; thus, cold and wet may act indirectly by causing overcrowding and close contact, want of fresh air and of proper ventilation, sore throats, and other catarrhal conditions. These conditions favour increase of the carrier rate, which, when it reaches a percentage of 20 (Glover), is followed by the appearance of cases of cerebro-spinal fever. This much appears fairly clear, but the further question arises as to the direct influence of meteorological conditions in favouring the systemic invasion by the meningococcus; in other words, of inducing a sudden outbreak of cases in epidemic form; this might depend on (*a*) diminished resistance of the individual or (*b*) increased virulence of the meningococcus.

As the winter (January to March) and spring are the periods of the year during which the disease is unusually prominent, *meteorological conditions* might naturally be expected to exert a definite influence on its incidence, and cerebro-spinal fever might be regarded as a weather disease; thus, east and north winds and a low temperature, especially sudden falls and oscillations of temperature, might by reducing the resistance of carriers and persons exposed to meningococcic infection lead to systemic infection. Sudden alterations in the atmospheric temperature have been

emphasised by Sophian[20] and Dopter[21] as responsible for the outbreak of cases, and I got the same impression when at the Royal Naval Hospital, Haslar, August, 1914–17, though, as will be seen below, a comparison of the incidence of the cases and the temperature conditions in the early months of 1915 did not justify this view. I investigated the points mentioned above in connexion with 93 cases occurring at large naval depôts during the first three months of 1915, but did not obtained results justifying a positive conclusion.[22]

From comparison of the monthly incidence of cerebro-spinal fever with the prevailing winds, it at first appeared that there was some evidence to support the preconceived view that northerly and easterly winds favour the occurrence of the disease. At Portsmouth, Plymouth, and Deal cases of the disease followed in the wake of north and east winds, but at Chatham no decided conclusion as to the influence of winds was forthcoming. The direction of the wind on (*a*) the day of onset of the disease; and (*b*) on the three previous days was then plotted out for 93 cases occurring at Portsmouth, Plymouth, Chatham, and Deal. On the actual day of onset the wind was more or less east or north in 50 cases, and south, west, or calm in 43. On the three days before the onset of the disease the wind was more or less east or north in 47, south or west in 35, and in 11 cases varied during the three days. On the whole, there is not sufficient evidence that east and north winds play an important part in causing an outbreak of the disease.

The question of the atmospheric temperature was gone into. In some, but not in all instances, the months with the lowest average daily temperature showed the largest number of cases of the disease, but the difference in the average daily temperatures was so comparatively small that no conclusion as to its influence is justified.

The influence of a sudden fall of temperature was next investigated. The temperatures (day and night) for three days before the onset of the disease in 93 cases from Portsmouth, Plymouth, Chatham, and Deal were examined in order to see if there was a sudden fall of temperature of 10° F. or more within this period. Out of the 93 cases there was such a fall in 37 only. There is, therefore, no reason to believe that a sudden fall of the atmospheric temperature causes an immediate outbreak of the disease.

On the other hand, from investigation of an epidemic at Hong-Kong in the early months of 1918 Olitsky[23] found that a sudden fall of temperature was followed in about four days by a great increase in the number of cases reported, and that absence of sunshine had the same effect.

Finally, an inquiry was made as to the relation between the prevailing wind and the average daily temperature combined and the incidence of cerebro-spinal fever. Consideration of the monthly incidences of 82 cases of cerebro-spinal fever with the prevailing winds and the average daily temperature for January to March at Portsmouth, Plymouth, Chatham, and Deal shows that 40 cases occurred in February, during which the prevailing wind was south-west and the average daily temperature 43·5°, whereas

in January (20 cases) the wind was west or south-west in the first half and north or north-east in the second half, and the average daily temperature 43·7°; in March (22 cases) the prevailing wind was north-east and the average daily temperature 45°. There was not, therefore, any real evidence that north and east winds and a low atmospheric temperature played a causal part in the outbreaks of cerebro-spinal fever.

Various Views on Effect of Weather Conditions.

According to Compton,[24] the conditions favouring invasion of the blood-stream by the meningococcus are a high degree of sudden saturation of the atmosphere with moisture and very little variation in the daily temperature of the air, the meningococcus being present; and Sophian states that during the outbreak of 2180 cases in New York in 1905 the weather was cold and wet. Olitsky, however, considered that humidity and rainfall did not exert any influence on the number of the cases. Closely connected with the humidity are the atmospheric pressure, the rainfall, and deficiency of sunlight; and 69 per cent. of Compton's cases occurred contemporaneously with a fall of the barometer, 91·5 per cent. with rain, and 82 per cent. with deficient sunshine. The high atmospheric humidity may conceivably act in several ways: (*a*) It may render the mucous membrane of the naso-pharynx more spongy and so more permeable to meningococci; (*b*) as the organism grows best in plenty of moisture at a temperature of 30° C. the inhalation of moist air, which slightly raises the bodily temperature, may provide the most favourable conditions for growth, it being well known that drying has a very depressing effect on the vitality of the meningococcus; (*c*) in addition, as a humid atmosphere diminishes evaporation and as a result of this the exudation of fluid from the nasal mucous membrane, the meningococci are less readily removed. On the other hand, from observations at Camp McClellan, Robey[25] came to the conclusion that cold and wet weather increased the carrier-rate and the incidence of cases on account of the closer contact of the men in the tents and mess-halls, and that, conversely, warm fresh air and sunlight had a powerful effect in diminishing the carrier-rate.

Sophian's analysis shows that most of the epidemics occur in exceptionally cold weather, but this relation is not constant, as some occur in quite mild conditions, and D)pter considers that continued cold is less provocative than sudden oscillations of temperature. In order to explain the simultaneous outbreak of cases of the disease in distant foci Netter and Debré[26] suggest that certain cosmic influences may combine to raise the virulence of the meningococcus, and that variations in its virulence comparable to those described for the pneumococcus occur.

In 1894 Herringham [27] showed that the meteorological conditions which when met with together caused an outbreak of pneumonia were (1) a wide daily range of temperature, (2) a dry condition of the air, and (3) an east wind. As these conditions do not, from what has been said, appear to bear a constant relation to the incidence of cerebro-spinal fever, it would be interesting to compare the curves of cerebro-spinal fever and pneumonia. This has been done by Newsholme,[28] who found that for three out of the four years of the war the curves closely corresponded, but that in July, 1918, there was an epidemic peak in the pneumonia curve but not in the cerebro-spinal curve. He concludes that the same winter and spring conditions favour the incidence of both. By plotting out the weekly mortality returns of the Registrar-General for the last few years I find that there was a corresponding rise in the incidence of cerebro-spinal fever in the early part of the year, but that the rise of pneumonia in the last two months of the year was not accompanied by a rise in the cerebro-spinal fever curve.

Unless it can be convincingly proved that the outbreaks of cerebro-spinal fever can be closely and accurately correlated with changes in the meteorological conditions—and that it is not so is clear from the confusing details just given—it becomes more probable that the conditions prevalent during the months of greatest incidence act by increasing the carrier-rate or the power of carriers to spread infection—namely, by coughing or by both means—and so exposing a larger number of possibly susceptible persons to the opportunity of systemic infection. Glover has shown that with a high carrier-rate the disease breaks out. The conditions favouring a high carrier-rate are (*a*) prevalence of colds and coughs, which enable existing carriers to infect others; (*b*) close contact of individuals such as occurs in cold weather. Overcrowding has been shown to be a factor of almost constant occurrence in outbreaks of the disease. Of course, neither catarrhal infections nor overcrowding is effective without the presence of carriers, but a varying number, 2–5 per cent., will always be found in any considerable collection of persons.

Dust.—The epidemic in 1907 at Leith occurred during cold, dry, dusty weather, and Robertson,[29] as Buchanan [30] had previously done in India, suggested that meningococcic infection may be due to air-borne dust. As it is now known that drying rapidly destroys the meningococcus, it would appear that the part, if any, played by dust is to set up cough, and so render carriers more active in the spread of the infection.

ÆTIOLOGY.

In this country our unpreparedness for war and the necessity for rapidly raising large armies led to overcrowding of the inadequate available barracks and depôts.

Overcrowding.

Overcrowding is well recognised as an important factor in the ætiology of cerebro-spinal fever and exerts its influence in several ways: it impairs the general health, favours the occurrence of various infections, especially influenza and catarrhal infections of the throat and upper respiratory passages, which may dispose to meningococcic invasion, and greatly increases the carrier-rate among the occupants of the crowded rooms.

Overcrowding in military barracks has been defined by Dr. J. A. Glover,[31] whose valuable deductions in relation to cerebro-spinal fever will be freely utilised, as the slightest excess over the mobilisation standard, which, as a rule, is an excess of 50 per cent. of the number of men allowed by the peace standard. The peace standard, according to the Royal Commission of 1861, provided 600 cubic feet per man and a space of one yard between the beds. The important points of overcrowding are the space between the beds and the efficiency of ventilation, the mere cubic space being an index rather than a vital factor. With the peace standard of one yard between the beds the percentage of meningococcic carriers is rarely more than 5, with the mobilisation standard of 1 ft. 4 in. between the beds the percentage of carriers may be 10, with a space less than 1 ft. 20, and when the space is less than 9 inches the carrier-rate is 28–30 per cent. Overcrowding increases the carrier-rate, the maximum being reached in three weeks; a carrier-rate of 20 per cent. is a danger-signal and is soon followed by the occurrence of cases of the disease and by a well-marked increase in the proportion of meningococci that are agglutinable. In January, 1918, at a certain military depôt, Glover found the carrier-rate both among contacts and non-contacts as high as 70 per cent. In such overcrowding the remedy of increasing the space between the beds to $2\frac{1}{2}$ feet is followed by a reduction in the carrier-rate, but not so rapidly as the rise due to overcrowding.

The experience of the American Expeditionary Force, for which I am indebted to the courtesy of Lieutenant-Colonel Haven Emerson, shows that the conditions of ocean transport involving great concentration of men in close, ill-ventilated quarters between decks and conditions contributing to a pronounced lowering of body resistance were responsible for the high incidence of the disease among the troops on

arriving at the disembarkation ports in France and Britain, for up to the stoppage of troop shipments in November, 1918, not less than 50 per cent. at all times, and frequently 80 per cent., of all the cases of cerebro-spinal fever reported among the American troops in Europe were in men within two weeks of landing.

Fatigue.

Fatigue is a factor of importance in causing outbreaks of the disease, and together with want of sleep and exposure reduces the bodily resistance and so opens the way to infection. Dopter[32] quotes a remarkable incident from the Versailles epidemic of 1839, during which out of a detachment of 153 recruits 79 developed the disease after a fatiguing march. He also refers to the increased frequency and mortality of the disease among recruits after forced marches during the European war, and points out that recruits suffer much more on account of their lack of training than soldiers of two or three years' service, though of the same age. Examination of the notes of naval cases shows that in a number of cases the disease began shortly after going on leave or returning to barracks; the fatigue of the journey may have played a causal part.

The Relation to Campaigns.

This question naturally arises in connexion with the great increase of the disease in this country since 1914. In the past it has not, like dysentery and enteric, been considered a war disease. Osler[33] points out that there is no reference to it in the Napoleonic, Crimean, Italian, or Danish wars, there were but a few cases in the Franco-Prussian, Russo-Japanese, and South African wars, though in the North and South American Civil War of 1861–3 there were outbreaks of moderate dimensions on both sides.

As there is little information as to the increased prevalence of the disease during previous wars, it may be interesting to quote the available details as to the present campaign. According to Galambos,[34] though there have been sporadic cases in the various theatres of war there have not been any epidemics among the German soldiers. In the French troops the disease has not, generally speaking, been common; in 1915 there were 1075 cases, or 4·3 per 10,000; in 1916 there were 451, or 1·8 per 10,000, and in 1917, 406, or 1·5 per 10,000. Dopter[35] explains the low incidence at the front by the open-air life and the comparative freedom from overcrowding, and contrasts the conditions with those in camps at the base.

By the kindness of the Director-General of the Army Medical Service I am enabled to say that the incidence in

the Army in this country was as follows: From Sept. 19th to Dec. 31st, 1914, 50 cases, with a mortality of 31, or 60 per cent.; during 1915, 1195 cases, with 586 deaths, or 49 per cent.; during 1916, 967 cases, with 430 deaths, or 44·6 per cent.; and during 1917, 1337 cases, with 593 deaths, or 44·3 per cent. In the British Expeditionary Force in France the disease began to appear widely in a scattered fashion, so that two cases hardly ever came from the same unit, in January, 1915, or at the same time as the troops in this country were attacked. Herringham [36] estimates that the outbreak in 1915, when, as in this country, the available serums were useless, was the worst, with a mortality of about 50 per cent., but that during the war the mortality probably never fell below 35 per cent. I am indebted to the courtesy of the Director-General of the Army Medical Service for the information that the annual ratio of cases of cerebro-spinal fever per 1000 admissions was 63 in 1915 and 31 in 1916. I am much indebted to Colonel J. G. Adami's lecture at the Royal Institution for the figures of the Canadian Expeditionary Force: out of a total of 420,000 officers and men from 1914 to 1918 there were 367 cases with a mortality of 198, or 54 per cent. Lieutenant-Colonel B. Myers has very kindly provided me with figures showing the monthly incidence among the New Zealand Expeditionary Force from July, 1917, to September, 1918; there were 75 cases with 24 deaths, or 32 per cent., among a strength varying from 14,000 to 21,000. Colonel R. J. Millard kindly informs me that among the Australian Force in the United Kingdom there were in 1916 65 cases with 29 deaths, or 44·6 per cent.; in 1917 out of an average strength of 64,431 officers and men 104 cases with 36, or 34·6 per cent., deaths; and in 1918 out of an average strength of 56,186 23 cases with 12, or 52 per cent., deaths.

In a list [37] of 42 diseases arranged in the order of their importance in causing days of sick wastage among the American Expeditionary Force during the year ending May 31st, 1918, meningitis and carriers were item No. 27. I am indebted to Lieutenant-Colonel Haven Emerson and Captain T. J. Duffield for the accompanying table.

During the war the disease first became prominent among the military population in this country, and then the civil population followed suit; the increase in the incidence of the civil cases during the war is striking: in 1915 the number of civil cases was eight times that of 1914, and in 1916 and 1917 four times that of 1914 (Reece).

That the greater incidence since the outbreak of war is due to some special conditions is obvious, and probably one of the most important is overcrowding in barracks; it is a disease not of the open campaign but of training camps, mobilisation centres, and depôts. This is to some extent borne out by the incidence of the disease in the Naval depôts as contrasted with ships, where, however, the life is by no

means the same as that in the field: among 509 cases in the Royal Navy during the first four years of the war 59, or 11·6 per cent., occurred in sea-going ships, and 363, or 71 per cent., at the large depôts at Portsmouth, Plymouth, Chatham, and Crystal Palace. But the comparatively low percentage of cases in ships may be due to other factors, such as the longer service of the men as compared with the

Incidence of Meningococcus Meningitis in U.S. Forces in France

Year.	Month.	Average strength.	No. of Cases.	Rate per 100,000.
1917	June.	7,180	0	0·0
,,	July.	16,055	5	31·2
,,	August.	27,708	5	18·0
,,	September.	50,100	5	10·0
,,	October.	75,475	5	6·6
,,	November.	107,875	40	37·1
,,	December.	151,498	27	17·8
1918	January.	196,591	33	16·8
,,	February.	231,602	51	22·0
,,	March.	283,405	35	12·4
,,	April.	372,843	49	13·1
,,	May.	541,543	61	11·3
,,	June.	772,817	40	5·2
,,	July.	1,034,177	34	3·3
,,	August.	1,310,233	58	4·4
,,	September.	1,634,457	143	8·7
,,	October.	1,811,402	526	29·0
,,	November.	1,925,206	204	10·6
,,	December.	1,909,252	235	12·3

new entries in barracks who form such a large proportion of the cases. Other unusual conditions bearing hardly on young soldiers are excessive fatigue, recurrent infections.

Recruits and New Entries.

The above are specially affected; thus in 1914–15, out of 15 cases at the Royal Naval Barracks, Devonport, 14 were new entries with an average service of 24 days (7 with less than 20 days' service). In 1916–17, out of 143 cases in the Navy, 31, or 21·7 per cent., occurred within three weeks of joining the service, and among 46 occurring in Portsmouth

further analysed by Fildes and Baker [38] 36, or 78 per cent., were new entries—namely, those who had been in the service for a few days or at most a few weeks. These authors, like Dopter, concluded that recent entry was a more important factor than age.

Occupation.—Recruits and young children are specially prone to be attacked; miners have also been stated to suffer more severely than other workers.

Trauma.—Blows on the head causing fracture of the base have been thought to play an important part by allowing a direct passage of meningococci from the naso-pharynx or sphenoidal sinus to the meninges. Short of fracture, it might reasonably be thought that any cranial damage or injury would, by diminishing resistance, favour the localisation and multiplication of meningococci present in the blood stream. There are comparatively few cases showing the sequence of cranial trauma and cerebro-spinal fever.

Antityphoid inoculation and ordinary *vaccination* have been followed by the disease and may, by reducing the resistance, favour infection. Antityphoid inoculation has been followed by a relapse, and it is possible that this may occur in abortive and latent cases of meningococcic infection. In the Navy vaccination is usually carried out shortly after entry, and, as mentioned elsewhere, the majority of the cases occur in new entries. Acting on the assumption that vaccination may be one of the factors favouring the incidence of the disease in new entries, vaccination has at times been postponed, but the disease has occurred in new entries who were not recently vaccinated or revaccinated.

Relation of Influenza and other Infections, especially Catarrhal Affections, to Cerebro-spinal Fever.

Influenza may be considered in relation to cerebro-spinal fever from three points of view: as specially related to it; as, in common with other diseases, depressing the resistance of the body and so rendering it liable to infection; or as, in common with other diseases of the respiratory tract, spreading the infection and increasing the carrier rate by coughing and sneezing.

From historical and epidemiological considerations Hamer [39] argues that cerebro-spinal fever is a sequel or complication of influenza, it being assumed that in special circumstances some individuals when attacked by influenza develop cerebro-spinal fever; he appears to believe that the meningococcus is not the cause of cerebro-spinal fever, although it may assume importance when activated by some "unknown influence" temporarily endowing it with virulence, and that

there is one common infecting agency for influenza, cerebro-spinal fever, poliomyelitis, and other epidemic diseases ; this appears to be his interpretation of the more ordinary view that the meningococcus is widely present in the throats of the general population, and at times undergoes enhanced virulence due to some unknown influence—telluric, climatic, or other. This broad view is so opposed to bacteriological concepts and to the general experience that it is difficult to entertain it without further and very convincing evidence. Bacteriologically it is true that cases of mixed infection with *B. influenzæ* and the meningococcus occasionally occur, as has been seen in the recent epidemic of influenza, Glover,[40] Whittingham,[41] and Fletcher[42] describing such cases without meningitis ; but this does not prove that the meningococcus and the influenza bacillus are the same or forms in the life-history of the same organism. From the historical and epidemiological point of view the evidence of the association of the diseases is not very convincing—at any rate, since the influenza pandemic of 1889, as, apart from the local epidemic in 1907, it is only since the outbreak of war that cerebro-spinal fever has been frequent in this country ; even since 1914 the association of the two diseases has not been constant.

In a diagram showing the four-weekly incidence of cerebro-spinal fever and of pneumonia in the British Army in the United Kingdom and the deaths from influenza in London during the four years 1915–18 Newsholme points out that there is a close correspondence in the curves of these three diseases during three out of the four years, and that there can be little doubt that the same spring and winter conditions favoured excess under all three headings ; but in July, 1918, there were epidemic peaks in the curves of influenza and pneumonia, but not in that of cerebro-spinal fever. Later on, however, Newsholme mentions that in 1915 there was an influenzal epidemic of low range in the eighth week of the year, and in 1916 a relatively small epidemic culminating in the last week of the year and terminating early in 1917. These outbreaks do not correspond exactly with those of cerebro-spinal fever, which were more severe in 1915 and (to a lesser degree) in 1917 than in 1916.

In the case of the Navy during 1918 there was a want of correspondence between the incidence of influenza and cerebro-spinal fever ; in May and June influenza was rife, but there was no rise in the curve of cerebro-spinal fever. Later in 1918 a more virulent epidemic of influenza occurred, and while this was in its early stage the number of naval cases of cerebro-spinal fever rose, so that in October there were 21 cases as compared with 3, 3, and 0 in the three previous years, and at one depôt where influenza was raging seven cases of cerebro-spinal fever occurred within a week. Another example of what appears to be a direct effect of influenza, namely, a local explosive outburst of cerebro-spinal

fever, may be mentioned; in February, 1919, among a number of naval officers in the same ward for influenza, eight cases of cerebro-spinal fever occurred in a few days. There was no known case of cerebro-spinal fever in the neighbourhood of the hospital, and presumably a carrier in the ward had become actively infective from the cough of influenza.

During the height of the influenza epidemic in October, 1918, there was a notable increase in the incidence of cerebro-spinal fever among the heavily infected (influenza and pneumonia) American troops arriving in France from the United States, as is shown in the figures already quoted. The second wave of influenza, in October, 1918, was much more severe in its complications and secondary infections, and it seems reasonable to explain the increased incidence of cerebro-spinal fever as the result of a lowering of the bodily resistance and an increased susceptibility to infection by the meningococcus.

The part played by influenza would then be analogous to that of other diseases and depressing conditions that have preceded and been thought to dispose to meningococcic infection, such as measles, rubella, mumps, and also menstruation in women, and the status lymphaticus. But as influenza may be overwhelmingly common it may be correspondingly more often followed by cerebro-spinal fever, and it would appear that when cerebro-spinal fever becomes more frequent or occurs in explosive outbursts after influenza the two obvious factors are impaired resistance and the presence of a chronic carrier with an influenzal cough which thereby facilitates the spread of meningococcic infection.

Colds and Catarrhal Affections.

The relation of colds and catarrhal affections to cerebro-spinal fever may be considered from two points of view: (*a*) The relation of preceding colds and catarrhal affections to individual cases of cerebro-spinal fever; and (*b*) the relation of the prevalence of colds and catarrhal affections to outbreaks of cerebro-spinal fever.

(*a*) Opinions differ widely as to an antecedent naso-pharyngeal catarrh in cases of cerebro-spinal fever, both as to its occurrence and when it is present as to its nature. Sophian believed that the meningococcus always causes a naso-pharyngitis, so that there is an initial catarrhal stage of the disease, and has been followed by Lundie, Thomas, Fleming, and MacLagan,[43] who recorded it as universal in 170 cases. Horder regards it as a cardinal symptom, and Herrick found it in a considerable proportion of his cases. On the other hand, it was present in very few of Sheffield Neave's 73 cases, in 25, or 40 per cent., of Worster-Drought and Kennedy's 62 cases, and is stated to be rare by Foster

and Gaskell. It is quite conceivable that naso-pharyngeal catarrh may dispose to infection by meningococci, and there is some evidence that adenoids, which are so commonly associated with naso-pharyngeal catarrh, favour infection (Rosenthal [44]). Cleminson [45] found that carriers on an average had 50 per cent. more adenoid tissue than normal subjects. C. Shearer [46] finds that nasal mucus favours the growth of meningococci ; this may depend on the presence of bodies of the type of accessory growth hormones (vitamines) which are present in blood, serum, and animal fluids, and have been shown by Miss D. Jordan Lloyd [47] to be necessary for the growth of the meningococcus in vitro. On the other hand, a profuse catarrhal discharge may remove the meningococcus before it can settle down on the inflamed surfaces (Crowe).

(*b*) The special Advisory Committee of the Medical Research Committee on the bacteriological studies of the epidemic in 1915 considered that the relation with catarrhs and the disease was fortuitous, as both have a similar seasonal prevalence, the relation being the same as that between catarrh and the prices of coal. On the other hand, the view that catarrhal throat affections by inducing coughing and sneezing spread meningococcic infection and so increase the carrier-rate and the chances of systemic infection, as urged by Pringle,[48] seems highly probable. The prevalence of colds in the population would thus favour the outbreak of cerebro-spinal fever, but it is not necessary that cerebro-spinal fever patients should have had colds or naso-pharyngitis.

Recent Acute Affections.

The depressing effect of recent acute infections, such as influenza, mumps, measles, has been mentioned as a probable factor in disposing persons to meningococcic infection ; this, however, is much less important than overcrowding. Among the naval cases previous acute disease, such as measles, rubella, and mumps, occurred in a small percentage only.

The sequence of events in the two following cases is perhaps worthy of mentioning. Two brothers from the Fair Isle, Shetland, had measles in September, 1915, in Haslar. One developed cerebro-spinal fever 13 days after the onset of measles and died. The other, who had never been well since the attack of measles, died in Haslar three months later from tuberculous meningitis. In both cases a necropsy was made.

Herrick lays stress on the occurrence of previous acute disease ; among his 208 cases 26 had recently had measles, 15 mumps, and among another series in another American

camp the percentage was almost the same—13 of measles and 8 of mumps among 112 cases (Miller and Martin [49]). The occurrence of meningococcic meningitis after mumps, in which a lymphocytic reaction of the meninges is extremely common, suggests that this disease may render the meninges particularly susceptible to infection. Symmers [50] found that the subjects of status lymphaticus were especially prone to meningococcic infection, and this may be correlated with H. C. Cameron's view that the status lymphaticus is the result of a chronic infective condition. But in their account of the Australian outbreak Fairley and Stewart [51] state that nearly all the patients were in good health before the attack and that the large number of fine young men struck down was most remarkable.

Influence of Age and Sex.

Age is an important ætiological factor; the most susceptible age is from birth to 5 years, and in some epidemics 80 to 90 per cent. of the patients have been under 15 years of age; in the Dantzic epidemic of 1865, for example, 93 per cent. were under this age. It is generally estimated that half the total cases occur in the first five years of life; in England and Wales during 1914 51·4 per cent. of the cases were in children under the age of 5 years and 72·4 per cent. under 10. But in 1915 and 1916 these percentages (30 and 48·8, and 38·7 and 54·8 respectively) were much lower, although the military cases are not included (Reece). Compton [52] connects the greater fragility and delicacy of the naso-pharyngeal mucosa in children with their susceptibility to infection. In a chart of 750 cases among the Chinese population at Hong-Kong the peaks of the curve of incidence were: (*a*) from infancy to 5 years; and (*b*) at the age of $17\frac{1}{2}$ years (Gale [53]). Though common in infants cerebro-spinal fever is rare during the first three months of life, and at this period meningitis is more often due to *B. coli* than to other micro-organisms; among 19 cases of meningitis in the newly born, collected by Barron, [54] one only was meningococcic, and among 20 more under the age of 3 months four were meningococcic. According to Compton [55] the least susceptible age is between 35 and 40 years. Children and recent recruits are the members of the community most frequently attacked, but in the case of the latter their environment rather than their age is the determining factor.

Sex in itself is often stated not to exert any influence on the incidence of the disease, but among the civil population during 1914, 1915, and 1916 Colonel Reece found that the total number of males exceeded that of females, the percentage of males being 57·7, 53·9, and 54·4 This predominance of male incidence was shown in practically all the age-periods; the exceptions were the age-group 20–30 in

1915 and 1916, and the age-group 30 and over for 1916. It seems probable that the abstraction of a large number of males from the civil population would explain this; at any rate, the incidence of attack on these age-groups would be far heavier on males than on females if the military and naval cases were included. In the epidemic of 1918 among the Chinese population of Hong-Kong males were attacked slightly more than twice as often as females. Why males, especially males in early life, are more prone to attack is not certainly known, but it is natural to explain it by their environment and greater liability to overcrowding.

Spread of Infection.

Granting that the meningococcus is the cause of cerebro-spinal fever and that so far man is the only recognised carrier, it follows that the disease is always conveyed by a healthy carrier or by a patient with the disease. Patients are almost always confined to bed and their sphere of infectivity thus much restricted, and the rarity with which one case can be traced to another proves that infection is usually due to contact with a healthy and often unrecognised carrier. Of the carriers, the chronic ones, who are commonly so in virtue of an infected accessory sinus, adenoids, or other focus, are much more powerful for harm than the ordinary carriers whose term of activity is usually not more than three weeks. Robey,[56] indeed, found that a chronic carrier can usually be found among the contacts of a case of the disease.

The actual spread of infection is mainly due to droplets expelled from the naso-pharynx in coughing, sneezing, and violent expiratory efforts, so that the carrier's power for harm depends on the existence of cough, &c., on the number of meningococci, and also largely on their being of an epidemic type. Infection may also be conveyed directly from mouth to mouth, as in kissing. The question of the importance of prostitutes as meningococcic carriers requires investigation. Other methods of spread of infection are less important or very doubtful. Adami[57] has recently advocated the spread of infection through the intermediation of drinking vessels, partially or imperfectly rinsed, in crowded canteens and refreshment booths. For this indirect method of infection carriers are of course necessary, unless it be assumed that the disease only passes from one case to another, and this is incompatible with the history of isolated cases. The spread of infection by sputum, through flies or insect carriers, or by clothing is improbable from the low vitality of the meningococcus and its rapid destruction by drying.

When a carrier lives in close contact with healthy individuals the carrier state is prone, especially under conditions of overcrowding, to be conveyed to others, and these new

carriers act in like manner. Among the individuals thus exposed some may, from diminished resistance, become systemically infected, and, as Glover has shown, this should be expected when the carrier-rate, which is normally under 5 per cent., rises to the danger-line of 20 per cent. That the infectivity of the meningococcus is low or the general resistance to it high is shown by the remarkable infrequency with which doctors and those in attendance on patients contract the disease and by the rarity of the spread of the disease when a patient is nursed in a general ward. It is said in explanation of the rarity with which nurses and attendants are infected that the meningococcus usually disappears from the naso-pharynx about the fifth day of the disease (Flügge).

The low infectivity is also shown by the generally acknowledged difficulty in tracing cases to contact with other cases and by the comparatively isolated incidence of the cases which occur sporadically more often than in groups. Thus, among 3617 cases in 1915 and 1916 Reece found that 3402 were single cases and 100 instances of multiple cases in a house; but occasionally several cases may occur in the same family; Scott [58] records four deaths in one day out of a family of seven children from fulminating cerebro-spinal fever. A number of cases may occur at the same time without any obvious connexion between them, as if due to some meteorological influence, though the presence of a dangerous and chronic carrier may very probably be the real explanation. The carrier-rate is from 10 to 20 times higher than the incidence of the disease.

The Path of Meningeal Invasion.

The path by which the meningococci reach the meninges has been thought to be (1) direct invasion of the cerebral meninges from the naso-pharynx and accessory sinuses via the lymphatics; (2) lymphogenous infection of the meninges along the spinal nerve-roots; and (3) invasion of the blood-stream by meningococci from the portal of entry in the naso-pharynx and, subsequently, infection of the meninges, for which the meningococci have a special predilection.

Direct Invasion from Naso-Pharynx and Accessory Sinuses.

As the meningococcus is relatively such a common inhabitant of the naso-pharynx the analogy of otitic meningitis naturally suggested the once widely held view that the infection spreads directly to the base of the brain. As far back as 1883 this view was originated by Weigert and Weichselbaum's observation that at necropsies the nasal

mucosa was inflamed and covered with muco-pus. The following routes have since been advocated :—

(*a*) Through the sphenoidal sinuses ; this was the early view of Westenhoeffer,[59] based on the observation that in one-third of 29 necropsies these sinuses showed inflammation ; subsequently, he gave up this opinion as a result of failure to discover meningococci in the substance of the sphenoid bone, and in 1909 Elser and Huntoon [60] also failed to find meningococci in the sections of the walls of the sphenoidal sinus and of the hypophyseal region of the skull. Recently, however, Embleton and Peters [61] described meningococci in the bony walls of the sphenoidal sinus and in the contained pus ; and Holden [62] recorded a case with the sphenoidal sinus full of muco-pus containing meningococci, osteomyelitis of the sphenoid, discharge of pus into the sella turcica, and periostitis over the area covered by the pons and pituitary. But in 25 necropsies Worster-Drought and Kennedy [63] were unable to find any evidence in support of the direct spread of infection from the sphenoidal sinuses, and they point out that when sphenoidal suppuration is associated with meningococcic meningitis it may be secondary.

(*b*) Transethmoidal route. Communications through the cribriform plate of the ethmoid, between prolongations of the pia-arachnoid and the lymphatics of the nose, allow the virus of acute poliomyelitis to pass between the naso-pharynx and the cerebral meninges. Flexner [64] found that when this virus is introduced into the naso-pharynx of experimental animals the disease results, and in 1917 considered that meningococci probably passed along the lymphatic connexions around the olfactory nerves, thus supporting the contention put forward by Netter and Debré [65] in 1911 that meningococci pass from the nose through these communications direct to the base of the brain. So far experimental proof is wanting ; Austrian [66] found that the introduction of meningococci into the naso-pharynx of rabbits did not cause meningeal infection either in normal conditions or even when the meninges had previously been irritated and rendered congested.

(*c*) Through the Eustachian tube to the middle ear and so to the brain. This route is rendered unlikely by the rarity of otitis media in cerebro-spinal fever, and by its late occurrence when it does occur. I have seen a mixed meningococcic infection in otitic meningitis, but this is quite exceptional.

Lymphogenous Infection along the Spinal Nerve Roots.

Lymphogenous infection of the spinal cord by the passage of meningococci along the lymphatics of the spinal nerve roots in the cervical, thoracic, and abdominal regions, resembling that described in some cases of Heine-Medin disease, was suggested by Stuart McDonald,[67] who was led to this conception by Greenfield's teaching that in tuberculous meningitis the cord lesions may be older than the cerebral. McDonald postulated spread of the meningococci to the cervical glands, to the lungs, or by swallowing to the intestines and mesenteric glands, and then extension along the perineural lymphatics to the meninges. Impressed with the frequency of enlarged and inflamed Peyer's patches in children dying of the disease, Radmann [68] considered that the intestine was the portal of entry.

Fowler [69] supported the view that cerebro-spinal fever is due to an acute abdominal infection on the grounds that (*a*) the spinal cord lesion is the oldest; (*b*) that the abdominal reflexes are abolished—evidence that the lower dorsal cord is affected; (*c*) that there was only a slight degree of cerebral disturbance in some of his cases; and (*d*) that exclusively breast-fed infants are not attacked. These arguments are open to considerable criticism. The frequency of intestinal catarrh, enlarged mesenteric glands, and swelling of the lymphatic tissue of the alimentary tract in necropsies on cases of cerebro-spinal fever might appear to be in favour of the view that the infection may enter through the gastro-intestinal tract. But the prevalence of these changes in animals experimentally infected through the meninges suggests that they are merely the result of the meningococcic infection, however produced (St. Clair Symmers [70]).

Infection from the Blood Stream.

Elser and Huntoon, Austrian, and Herrick,[71] who on the grounds of morbid anatomy, experimental research and clinical observations opposed the view that meningeal infection occurs by direct extension from the naso-pharynx and accessory sinuses, argue that the meningococci pass into the blood stream, and thus reach the meninges, especially the choroid plexuses of the lateral ventricles. In fact, that, as in tuberculous meningitis, there is first a local focus, then a general blood infection, and, lastly, a meningeal metastasis; the main difference being that in cerebro-spinal fever the local reservoir of the meningococci is a saprophytic collection in the naso-pharynx. The sequence of events is exactly parallel to that postulated by Draper and others in acute poliomyelitis—namely, naso-pharyngeal entry, general

hæmic infection with later localisation in the central nervous system.

The evidence for infection of the meninges from the general circulation is not, as Horder [72] points out, conclusive. In favour of this view, which is widely gaining ground, is the clinical evidence of a general infection—namely, symptoms resembling those of pneumonia or influenza, before the onset of meningitic manifestations. The pre-meningitic symptoms usually last for a few hours to two days, but may persist much longer (intermittent meningococcic fever), and in some cases of proved meningococcic septicæmia, as in the fulminating and abortive types, meningitis never supervenes. This conception of cerebro-spinal fever recalls the late Dr. Gee's aphorism [73] of nearly a quarter of a century ago that "Pneumonia is not a local, but a general disease; and the brunt of it may fall upon any part—lungs, membranes of the brain, intestines, kidneys."

Herrick recognised the pre-meningitic stage in 45 per cent. of 265 cases, and states that with special technique positive blood cultures can be obtained in 50 to 80 per cent. of cases examined at an early stage. Baeslack [74] obtained positive results in 36 per cent. of early cases, but other observers find that the percentage of blood cultures is not more than 25; and it is assumed that in the ordinary run of cases the blood, though it conveys the meningococcus to the meninges, does not become infected. As an example of the transient nature of the meningococcæmia, attention may be directed to Maxcy's [75] observations of a positive blood culture followed after the short interval of five hours by a negative result.

Huntoon and Elser point out that in meningitis due to extension from ear, mastoid, or antral infection the onset is gradual, whereas in experimental meningitis due to hæmic infection the onset is sudden, so that the acute mode of onset in meningococcic meningitis is in favour of infection by the blood stream. As a further argument in favour of the pre-meningitic septicæmia Herrick instances the success of intravenous injection of serum; and it may be added that the petechial rash seen soon after the onset of general septicæmic symptoms has been found to contain meningococci (Netter,[76] Blanchier [77]).

Some light is thrown on the question why meningitis does not supervene in every case of meningococcæmia, for example, in the abortive, solely purpuric, and the prolonged septicæmic cases, by Austrian's experiments. He found that in rabbits with meningococci injected into the blood meningitis did not supervene unless the congestion of the meninges was induced by the intrathecal injection of horse serum. It may thus be supposed that in cases of cerebro-spinal fever the resistance of the choroid plexuses and meninges is intrinsically low, or that it is diminished by

some extraneous factor, or that after a time the meningococcic endotoxin is sufficiently concentrated to damage the meninges and render them permeable to meningococci.

While the hæmic infection of the meninges appears to be applicable to the majority of the cases, the possibility that in certain instances infection may pass by other routes, such as through the cribriform plate of the ethmoid or the sphenoid, should not be entirely excluded. In connexion with the path of infection of the meninges the question arises where the meningitis begins, whether it starts in the choroid plexuses of the lateral ventricles, as seems to be the general view, in the spinal meninges, or in both situations simultaneously. That the meningococci first attack the choroid plexus is supported by the observation that lumbar puncture, when repeated at short intervals, may eventually bring down meningococci by drainage, and that in some fulminant cases the cerebro-spinal fluid obtained during life is free from meningococci, though after death meningococci are found in the lateral ventricles (W. W. Herrick). On the other hand, if the meningitis always spread downwards from the brain to the cord it would be natural to expect that rigidity and retraction of the neck would constantly precede Kernig's sign, that is, if the view that this sign is due to irritation of the posterior nerve roots and not to increased intraventricular pressure be correct. In many instances this sequence holds good, but by no means in all. Again, in some instances lumbar puncture first yields turbid fluid and subsequently clear fluid, or the reverse of that regarded as suggesting that the choroid plexuses of the lateral ventricles are involved before the spinal meninges. In some necropsies the appearances are compatible with the view that the cerebral and spinal meninges are attacked simultaneously, and Ormerod [78] considers this more frequent than is ordinarily thought. Probably cerebral infection through the choroid plexuses is the usual though not exclusive site of initial invasion.

Meningococcic Septicæmia.

This condition may present several variations from the short initial invasion of the blood by meningococci, which probably precedes infection of the meninges in most, if not all, of the cases of meningococcic meningitis. Possibly cases of true meningococcic septicæmia are only more commonly recognised now than formerly, but Netter [79] has suggested that Dopter's observation that whereas before the war 96 per cent. of the cases of meningococcic meningitis were infected with the meningococcic Type A (Gordon's I. and III. types), a change has taken place, so that now the parameningo coccus, or Type B (Gordon's II. and IV.) is responsible for an equal, if not a larger, number of the cases, may be correlated with an increased incidence of meningococcæmia and

meningococcic manifestations in the skin, joints, and eyes. Brulé [80] also considers that parameningococcæmia (due to Type B) is more frequent and more severe than meningococcæmia (due to Type A).

Meningococcæmia appears to have been first established by Gwyn [81] in 1899 in a case of meningitis with arthritis. Salomon [82] in 1902 detected meningococci in the blood eight weeks before meningitis supervened ; in the following year Warfield and Walker [83] described the first case of meningococcic endocarditis with septicæmia ; a fulminating case of meningococcæmia also without meningitis was recorded by Andrewes [84] in 1906, and in reviewing the cases two years later Duval [85] summed up in favour of the septicæmia being secondary to the meningitis, the reverse of the present opinion. Lüdke [86] described a case of meningococcic septicæmia in which in addition streptococci were obtained by blood culture.

Portret [87] distinguished four kinds of meningococcæmia : (I.) without meningitis, (II.) preceding meningitis, (III.) with metastases, (IV.) without metastases. The following forms of meningococcic septicæmia may be described :—

1. In a certain number of cases a *fulminating meningococcæmia* proves fatal before any meningitis has had time to occur, and lumbar puncture, if performed, gives exit to clear fluid without any meningococci or increased cell content. At the necropsy meningococci can perhaps be obtained from the fluid in the lateral ventricles of the brain, but there is no exudation. The clinical features of these cases are severe toxæmia often at the onset with a low temperature followed by fever and perhaps hyperpyrexia, rapid pulse and respirations, and extensive hæmorrhages into the skin, mucous and serous membranes, and adrenals. The clinical picture may suggest the "acute abdomen" such as internal strangulation, intussusception (Pybus [88]) or Henoch's purpura, fulminating purpura, hæmorrhagic fevers.

2. Abortive cases in which a blood infection is overcome after a short time by natural immunity, though commonly assumed to be frequent, are difficult to prove. Cases of febrile meningococcic purpura without meningeal symptoms, or presenting meningeal irritation which, as shown by lumbar puncture, is not due to meningitis and may therefore be explained as meningism, come under this heading. Sainton and Maille's [89] case with a measly eruption, synovitis of two joints containing meningococci, and a positive blood culture but no meningitic symptoms, the whole illness lasting about a week, belongs to this group of abortive cases. In order to determine the incidence of these abortive cases during an epidemic [90] Maxcy selected 27 cases with fever, headache, and malaise, but without petechiæ, and made blood cultures which were uniformly negative.

Doubt is thus thrown on the assumption of their frequency, but further investigations of this character are desirable.

3. Intermittent meningococcic fever due to septicæmia may (*a*) last for weeks without any meningitic symptoms ever developing, or (*b*) it may follow meningitis, or (*c*) show transient meningitic symptoms, or (*d*) terminate in meningitis.

(*a*) Some cases have septicæmia for weeks or months and meningitis never occurs. In Liebermeister's [91] case the disease lasted four months and in Bray's [92] case, complicated by chronic pulmonary tuberculosis, there was fever for five months and recognised meningococcæmia for three months. Though striking, they have not been very often recognised: Netter [93] had five examples among his 368 cases, and Brette [94] collected 22 cases in 1918. The attacks of fever may be quotidian or tertian and in the intervals the patient may feel well. The disease may resemble malaria, quotidian or tertian, or enteric fever—Netter's [95] pseudo-malarial and pseudo-typhoid forms. The attacks of fever may begin with a rigor and end with sweating, be accompanied by splenic enlargement; joint pains and orchitis may occur, and rashes, such as polymorphic erythema or erythema nodosum, herpes or papules, especially on the lower extremities or around the joints, or petechiæ may be present. But the disease may run its course without any cutaneous manifestations (Zeissler and Reidel, [96] Worster-Drought and Kennedy [97]). In exceptional instances malignant endocarditis is due to infection with the meningococcus (Warfield and Walker, Cecil and Soper, [98] Worster-Drought and Kennedy.)

(*b*) In another group septicæmia follows the subsidence of meningococcic meningitis. Brulé [99] records a case with septicæmia of two months' duration with purpura and positive blood cultures on five occasions. Lancelin's [100] patient had meningococcic meningitis, and after an afebrile period of four days had fever imitating malaria for seven days and then yielded to serum; meningococci were not obtained from the blood, but the presence of purpura rendered septicæmia highly probable. Among 126 cases Landry and Hamley [101] detected two cases of post-meningitic septicæmia. If blood cultures were more often done in chronic cases septicæmia would probably be shown to be comparatively common.

(*c*) During the course of intermittent meningococcic fever there may be transient meningitic symptoms; thus, Maxcy describes a case with transient rigidity of the neck, which appeared a week after the onset and rapidly passed off.

(*d*) In an allied group of cases the septicæmia is prolonged, but is eventually followed by meningeal infection;

in Ainé and Chéné's[102] case the pseudo-malarial stage with splenic enlargement lasted for four weeks before the onset of meningitis; and in Serr and Brette's[103] two cases lumbar puncture was first performed after four and two months' fever, and cures rapidly followed the intravenous injection of serum.

A correct diagnosis is seldom made in the absence of meningitic symptoms. Blood cultures should be taken during the febrile paroxysm.

In Cantieri's[104] case the first meningitic symptoms appeared on the eighty-first day of the disease, and by this time the following diagnoses had been made: intermittent fever, Addison's disease, tuberculosis, Mediterranean fever, septicæmia, and syphilitic fever.

References to Lecture I.

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LECTURE II.

CLINICAL PICTURE.

Incubation.

Mr. President, Censors, and Fellows of the College, —The incubation period has been variously stated to be from one day up to as long an interval as 30 days, most writers inclining to a period of four or five days, and very few regarding it as long as 10 days. These estimates have been based on the interval between known contact with a case or a recognised carrier and the appearance of symptoms, but the cases with an apparently long incubation period are open to the fallacy that they may have come in contact with an unknown carrier in the interval. A more accurate basis for deciding the incubation period would be provided by determining the average duration of the period that meningococci are present in the naso-pharynx before symptoms of systemic infection appear. There are not many observations bearing on this point. It is generally agreed that the disease very rarely attacks carriers; and chronic carriers, as shown by Gates,[37] contain immune bodies in the blood and so may be regarded as more or less protected. Among 485 carriers under the observation of Fildes and Baker[30] no case of cerebro-spinal fever occurred; and these writers, having examined with a negative result 26 men who subsequently contracted the disease, conclude that carriers seldom develop the disease, and that the period of time between the acquisition of the meningococcus and the onset of the disease must usually be short. Out of these 26 cases five were examined within a week of the onset, eight during the second week, and four in the third week before the onset. The general opinion, as voiced by von Lingelsheim, Gordon, and Andrewes, is that meningococci are constantly present in the throat at the onset of the disease, and that every case arises in a carrier. Fildes and Baker's observations, as far as they go, are certainly compatible with the view that the incubation period is very short and need not be more than a day or two, but their failure to find any meningococci in the throats of persons who afterwards contracted the disease is exceptional, for other observers

with much smaller series of cases have usually been able to point to some examples of known carriers contracting the disease; thus, among Martin Flack's[32] 185 carriers 4 developed the disease during isolation.

Onset.

The usual onset is much like that of ordinary "influenza," and is sudden, with headache, fever, and vomiting, the symptoms becoming progressively worse, so that in 24 hours meningitis is suggested. Sometimes after this mode of onset the symptoms rather suddenly advance, so that in a short time—an hour or two—the patient is comatose or delirious; in young children, and occasionally in adults, the onset may be marked by convulsions. On the other hand, after the onset there may be a fallacious improvement for a day or two, as if the blood invasion were yielding to the forces of natural immunity, and then meningitic symptoms appear. The catarrhal onset lasting some days is more gradual, and it is a question whether the meningococcic invasion is superimposed on an ordinary catarrh or whether the catarrh is the first manifestation of meningococcic invasion of the throat—the first or catarrhal stage of cerebro-spinal fever described by some writers.

The acute or fulminating onset is the least frequent; it may take various forms. It may be maniacal, imitating delirium tremens, attended by convulsions suggesting epilepsy, by hallucinations or syncope, or the patient may be unconscious when first seen. In patients found unconscious, or in the apoplectic mode of onset, the diagnosis is obviously very difficult; in some instances the patient has fallen out of bed or out of his hammock, and the question of fractured base has arisen. This apoplectiform onset may be rapidly followed by death, and thus accounts for cases of sudden death unexplained until examination after death shows the presence of the meningococci in the central nervous system.

With severe hæmic infection the manifestations are those of grave toxæmia, approaching the typhoid state, often at the outset with a subnormal temperature, which subsequently rises rapidly, quick pulse and respirations, vomiting, and a hæmorrhagic rash. Sudden cardiac collapse and fatal syncope at the onset of meningitis are specially described by Sainton.[98] The initial shock may be considerable, and when accompanied by vomiting, abdominal pain, and diarrhœa may suggest an acute abdominal lesion such as appendicitis or perforation, and laparotomy has naturally been performed (St. Clair Symmers[105]). One such case in the Navy was operated upon for a supposed perforated gastric ulcer and found to have a normal abdomen; at the suggestion of the anæsthetist, Temporary Surgeon Commander C. W. Morris, lumbar puncture was at once performed and

turbid fluid containing meningococci obtained. The association of a hæmorrhagic rash with an acute abdominal onset may present the clinical picture of Henoch's purpura.

The occurrence of cases with this abdominal onset might, perhaps, suggest that infection entered through the alimentary canal, but the frequency with which the medulla of the adrenals is disorganised with hæmorrhage would satisfactorily explain the collapse, and by stimulation of the adjacent sympathetic plexus the acute abdominal symptoms; this interpretation gains support from the acute abdominal crises occasionally seen in Addison's disease. It should be added that alarming collapse may be induced by moving the patient to hospital.

Clinical Forms.

The manifestations are protean and as a result of differences in the clinical features numerous forms have been described, mainly on the basis of the rate at which the disease runs its course. Cerebro-spinal fever, like acute poliomyelitis, has two distinct phases: (*a*) the general or systemic infection; and (*b*) the localisation in the meninges. The evidence of systemic infection is usually prominent in the initial stages and the process is then commonly extremely acute, but it may continue for weeks, and in rather rare instances chronic septicæmia follows meningitis.

A most important factor influencing the course and type of the disease is the serum treatment. Absence of or inefficient serum treatment is responsible for fatal results either early in the disease or after a chronic illness due to adhesions or chronic septicæmia. The different types of cerebro-spinal fever show transitional forms, and description of the forms is apt to be artificial and confusing, as a single case may appear to belong to two. Further, the clinical picture of the disease is often abruptly changed by unexpected alterations, such as improvement or the onset of grave symptoms. The following forms of cerebro-spinal fever will be briefly mentioned without a detailed description, and to avoid repetition the symptoms will be mainly dealt with subsequently: (1) fulminating; (2) ordinary acute; (3) abortive; (4) chronic: (*a*) septicæmic, (*b*) encysted or loculated meningitis, variety posterior basic meningitis of infants.

Fulminating Form.

Fulminating cases, fatal within 48 hours or less from the onset, are extremely dramatic and from their rapid course are often of medico-legal interest and the subjects of inquests. These cases are said to be more frequent early in the course of epidemics. The onset is sudden with sym-

ptoms of intense poisoning, collapse, vomiting, and severe headache. A purpuric eruption is almost constant, the hæmorrhagic areas sometimes increasing so rapidly in size that their progress can be watched with the eye; but labial herpes, which usually appears on the fourth day of the disease, is hardly ever seen. Diarrhœa, acute abdominal pain, and coffee-ground vomit from the gastric extravasations are occasionally present.[46] Headache may be absent, and the temperature, though usually raised, may be low as the result of the collapse. A peculiar smell has been described (Neave [70]), but I have not noticed it.

Two groups of fulminating cases with transitions between them have been described, especially by MacLagan [66]: (1) the purely septicæmic cases without meningitis characterised by rigors, prostration, cyanosis, cardiac failure, and mental clearness to the end; and (2) the cases with purulent meningitis in which unconsciousness rapidly sets in and passes into coma. In a number of fulminating cases meningococci, though not found in the cerebro-spinal fluid drawn off during life, can be isolated from the cerebral ventricles or base of the brain after death, thus showing the transition from the general to the local infection. The most rapidly fatal cases are those with general infection only. Purpura occurs in both, and the symptoms of collapse have been correlated with the hæmorrhagic condition of the adrenal medulla, for which, as for the other nervous tissues, the meningococcus has a predilection (MacLagan).

The fulminating cases have been thought to be less often seen in young children and infants than in older persons, but possibly some at any rate of the rapidly fatal cases of adrenal hæmorrhage in infants are of this nature. Andrewes,[3] finding the adrenals sterile bacteriologically, suggested the possibility of hæmorrhagic small-pox, but some of those less thoroughly examined may have been meningococcic. In the fulminating cases meningococci may be found in the blood by smears or blood cultures, and the proper treatment is intravenous injection of serum in large quantities.

Ordinary Acute Form.

The ordinary acute cases pass by transitions into those called by Netter and Debré [76] the hyperacute on the one hand and into the mild cases on the other. The onset is sudden, and after a short interval meningitic symptoms appear—stiffness and retraction of the neck, very violent headache, Kernig's sign—and a state of cerebral irritation supervenes, passing if unrelieved by treatment into coma. Energetic treatment has a dramatic effect, but recrudescences of the symptoms from reinfection, either from the naso-pharynx or from some localised focus in the meninges which

is not reached by the intrathecal injection of serum, may occur. Some cases, because the treatment is begun late or is not efficient, become chronic from the formation of adhesions, obstruction of the cerebral ventricles, and hydrocephalus.

Abortive Forms.

The word "abortive" has been employed in two different ways:—

(*a*) As applied to cases in which the cerebro-spinal fever does not go any further than the septicæmic stage, the blood infection subsiding under the influence of natural immunity before meningeal invasion occurs, so that in 24 to 48 hours the illness may be quite over. These cases are analogous to the frequent abortive cases of acute poliomyelitis. This is the sense in which the term "abortive" has more recently been employed. Clinically these cases may appear as febrile purpura, a form described elsewhere. Herrick refers to a case with the clinical features of a subacute polyarthritis, and says that there may be meningism. Abortive meningococcæmia was discussed in the first lecture.

(*b*) As describing abortive meningitis, the symptoms, though appearing suddenly, rapidly subside after two to six days. It is in this sense that "abortive" is used by Netter and Debré and by various British writers. These cases are prone to relapse. Abortive cases appear to be more frequent towards the end of epidemics, possibly because they are then more easily detected. Culpin [22] described very mild cases characterised by slow pulse, and says that the cerebro-spinal fluid may be lymphocytic and show an occasional meningococcus or be negative.

Chronic Forms.

The chronic forms of cerebro-spinal fever may be divided into (1) cases which are not treated, or, if treated, do not receive the appropriate serum so that the meningococcic infection continues unaffected; (2) cases with meningococcic septicæmia which may precede, follow, or occur without meningeal infection; these conditions were described in the first lecture; (3) cases with meningitic adhesions and obstruction to the free circulation of cerebro-spinal fluid, so that parts of the cerebro-spinal subarachnoid space or the cerebral ventricles become cut off and form closed cavities inaccessible to serum injected intrathecally in the ordinary way. This encysted or loculated form of meningococcic meningitis, of which posterior basic meningitis of infants is a variety, probably accounts for most of the chronic cases,

and as the adhesions are likely to form if serum treatment be delayed or inefficient it may include many of the chronic cases mentioned above in which the serum treatment has for one cause or another not been successful.

Encysted, loculated meningitis; closed ventricular meningitis; ventriculitis; ependymitis; pyocephaly; hydrocephalus.—These various names are applied to loculation or shutting off of some part of the space containing the cerebro-spinal fluid. As a result of a large quantity of fibrin the spinal subarachnoid space may be divided into two parts; the lower one can be drained by ordinary lumbar puncture and the meningococcic infection brought under the influence of antimeningococcic serum, whereas in the part above the obstruction the meningitis continues and keeps up the symptoms. This condition is characterised by a want of correspondence between the character of the cerebro-spinal fluid, which may be clear, free from meningococci, or obtainable in a few drops only, and the symptoms which persist. Lumbar puncture performed above the obstruction gives exit to turbid cerebro-spinal fluid containing meningococci.

More often meningitis seals the communications—the foramina of Magendie and Luschka—between the ventricles and the subarachnoid space, and as a result the ventricles, if infected (ependymitis), become distended with turbid fluid or pus which may be extremely thick (pyocephaly), or, if not infected or the infection dies out, simply show chronic hydrocephalus with clear sterile fluid. Very rarely cerebral or subdural abscesses containing meningococci may be found; Hallez [42] mentions three examples. On account of the small size of the foramina and the frequency of delay in diagnosis and treatment in the very young blocking of the ventricular exits is more likely to occur in infants and children than in adults. An interesting point arises as to the time that it takes for the obstruction to the ventricular foramina to be established; usually the symptoms do not appear until the primary acute attack is subsiding or is over, but they may begin quite early, and possibly in some instances the meningococcic infection starts in, and is confined to, the choroid plexuses of the lateral ventricles, the spread of infection being prevented by rapid closure of the foramina. In rare instances one lateral ventricle only is dilated.

In cases with closed infected cerebral ventricles lumbar puncture and intrathecal injection of antimeningococcic serum may cure the spinal meningitis but cannot influence the meningococcic infection of the cerebral ventricles. On lumbar puncture the cerebro-spinal fluid may be small in amount, at the most not more than 20 c.cm., or there may be none. The fluid may be clear with a predominance of lymphocytes and a normal power of reducing Fehling's solution, and does not correspond to the degree of the clinical symptoms, thus showing that there is not an ordinary

recrudescence of the cerebro-spinal meningitis. In spite of intensive intrathecal serum treatment the symptoms characteristic of ventricular infection and distension persist; these are excessive wasting, although the patient may take food well, bedsores, incontinence of urine and fæces, headache, vomiting, mental torpor passing into semi-coma, hyperæsthesia, Macewen's sign, rigidity and contractions, paralyses, diminution or loss of vision and hearing, nystagmus, dilated and sluggish pupils, and irregularities of respiration. The temperature varies; it may be intermittent, with wide oscillations or crises, or irregular, or there may be no fever at all. The symptoms may show remarkable intermissions. Patients with encysted meningitis may react violently to injections of serum given in the site of an ordinary lumbar puncture, with appalling headache ascribed to engorgement of the choroid plexuses and increased intraventricular pressure. The outlook is bad unless the shut-off spaces be tapped, and when there is meningococcic infection serum injected; but sometimes, although the course is long with repeated lumbar punctures, the obstruction of the foramina of the ventricles spontaneously passes off, causing relief of the symptoms.

The preventive treatment is the early start of vigorous and effective serum treatment. Measures to prevent blocking of the subarachnoid space and the formation of adhesions are washing out the intrathecal space with saline or solution of sodium citrate before the injection of serum. The treatment, puncture of the ventricles, and injection of serum in case of ependymitis, and drainage alone in aseptic hydrocephalus is mentioned elsewhere.

Posterior basic meningitis of infants is chronic encysted meningococcic meningitis in young infants, and its special features appear to depend on the early age of the patients rather than on any peculiarity in the infecting organism. More than 20 years ago Still[103] showed that the disease was due to a micro-organism almost identical with the meningococcus, and of late years it has become recognised that there is no constant bacteriological distinction between the meningococcus of posterior basic meningitis and that of cerebro-spinal fever in later life. But Andrewes[4] states that serologically the meningococci may be of a different strain from those of the epidemic disease in adults, and Lieutenant-Colonel M. H. Gordon kindly informs me that the meningococci in posterior basic meningitis do not differ serologically from those in adult cases, except that some, which are more difficult to identify, are usually atypical specimens of his Group IV.

With regard to the modifying influence of age, it is, of course, the rule that infections run a more rapid course in early that in late life, but it has seemed to me that both

meningococcic and tuberculous meningitis are exceptional in the more rapid course in adults than in infants. This may to some extent depend on the expansile skull of the infant which prevents the intracranial and intraventricular pressure from becoming excessive so rapidly as in the adult or adolescent. Among the cases called posterior basic meningitis half occur under six months of age, three-quarters within the first year, and practically all under the age of two years, but there is no essential difference between the condition of closed meningococcic infection of the cerebral ventricles in infants and in adults.

The disease is sporadic and may arise at any time of the year, but, as in later life, most of the cases occur in the first half of the year; among F. E. Batten's [6] 85 cases, 54, or 63·5 per cent., occurred during the first five months of the year. Though a matter of common knowledge, the disease is not very common; thus, writing in 1898, Still found that at the Hospital for Sick Children, Great Ormond-street, during the previous ten years, a period when the disease must have been exciting much attention, 49 cases only came to necropsy.

It may be well to mention the main clinical features differentiating the clinical form called posterior basic meningitis from ordinary cerebro-spinal fever in adults: 1. The chronicity of the disease, for acute cases of meningococcic meningitis do not come under this heading. 2. The rarity of eruptions; among Hildesheim's [47] 100 cases there was no example of a purpuric rash, and herpes was present in two cases only. In November, 1918, Dr. Claude Ker showed me a case of posterior basic meningitis of three months' duration with profuse infra-orbital herpes during a recrudescence. An ill-defined erythema occurs in a few cases. 3. Amaurosis or loss of vision without objective changes in the retina or optic nerve is common; it was noted in 37 out of Hildesheim's 100 cases. 4. The rarity of deafness and the occasional presence of auditory hyperacuity. 5. The prominence of opisthotonos, due to the greater flexibility of the spinal column. 6. Joint infection appears to be usually peri-arthritic rather than intra-arthritic, and may be associated with pseudo-glioma or the opacity of the vitreous caused by meningococcic invasion and imitating a glioma.

In the early stages the disease may be very difficult to recognise, as fever, tremor of the limbs, and some bulging of the anterior fontanelle may be the only symptoms. In such cases Zingher [113] urges that a dry or sterile lumbar puncture should be the indication for tapping the ventricles and daily intraventricular injection of serum until the fluid is sterile. According to Batten, 50 per cent. of the patients survive, and of these 15 per cent. recover completely, while the remaining 35 per cent. are left with blindness, hydrocephalus, and varying degrees of mental deficiency.

Cerebro-spinal Fluid.

The characters of the cerebro-spinal fluid vary at different periods of the disease, and changes in its naked-eye appearances may occur rapidly. During the first 24 hours the fluid may be perfectly clear; according to Netter and Debré this holds good in 75 per cent. of the cases. The clear fluid may be free from meningococci, the pre-meningitic or septicæmic stage, but it may, as shown by films and especially by culture, contain meningococci. Although the fluid first drawn off may be free from meningococci, that coming off a little later from the cranial or ventricular cavities may show meningococci. In other instances the fluid, though at first turbid, is subsequently clear, as if the meningitis started in the region of the cord rather than, as is probably usually the case, in the choroid plexuses of the lateral ventricles. The pressure is increased, but this may also occur in meningism and it is reasonable to believe that in the earliest stages of cerebro-spinal fever there may be meningism or toxic irritation of the meninges without microbic invasion.

The turbidity of the cerebro-spinal fluid varies from opalescence to very thick pus running with difficulty through the trocar. Admixture with blood is nearly always due to trauma during lumbar punctures, and in such cases the fluid at subsequent punctures is yellow from changes in the hæmoglobin (erythrochromia). In some instances a golden yellow cerebro-spinal fluid contains so much protein that it coagulates at once (Froin's syndrome); this is explained by Hanes [43] as due to stasis of the cerebro-spinal fluid in a cul-de-sac of the meninges with escape of blood plasma from the damaged blood-vessels of the pia-arachnoid, this xanthochromia being different from erythrochromia in which the remains of red blood corpuscles can be seen. A yellow colour is also seen in chronic cases with intrathecal adhesions preventing the passage of serum to the skull; lumbar puncture a day or two later gives exit to the serum which has this yellow tinge (Chiray [17]). The outlook in cases with adhesions is bad, and Forbes and Adam [35] found that the cases with Froin's syndrome were all fatal. Clotting after withdrawal, apart from that due to accidental admixture with blood, is evidence of some form of meningitis, and has been minutely studied by Connal.[19] It appears with the slightest opacity, varies with the degree of turbidity, and persists after the fluid has become practically clear. He describes several varieties of clot in meningococcic meningitis, which are always softer and more friable than in the tuberculous form.

The intrathecal pressure is greatest in the early stages of the disease, and gradually falls with the amelioration of the symptoms. But in the late stages of hydrocephalus, and

when there are adhesions cutting off the lower from the upper parts of the intrathecal space, little cerebro-spinal fluid can be withdrawn by lumbar puncture.

Chemical Characters.

Chemically albumin is absent from normal cerebro-spinal fluid, but appears as the result of meningitis, and its amount is a prognostic index, a small content in the early stages pointing to a mild attack and an increasing quantity causing anxiety. In the acute stage the quantity of albumin is large and fluctuates, whereas in chronic cases it is less and does not vary so much (Connal). The globulin present normally in minute quantities in cerebro-spinal fluid is increased in meningitis.

The reducing power of the normal fluid is usually lost; this has been explained as due to fermentation of the dextrose by the meningococci with liberation of lactic acid and a diminution in the alkalinity of the cerebro-spinal fluid (Connal), and it has been stated that in aseptic purulent meningitis the reducing power of the cerebro-spinal fluid is not affected. This, however, is disputed by Weissenbach and Mestrezat,[110] who find that diminution or loss of the reducing power varies directly with the cell content of the cerebro-spinal fluid, thus suggesting that the advent of leucocytes is responsible for the fall in the glucose content of the cerebro-spinal fluid.

Weil [109] finds that irritation of the meninges, however induced, and the resulting congestion are always accompanied by an increase in the glucose content of the cerebro-spinal fluid; this is what would occur in meningism. But if the irritation be of microbic origin the amount of glucose is diminished. Hence the glucose content varies at different stages of the disease; very early in the course of cerebro-spinal fever when the cerebro-spinal fluid is clear the glucose content is increased; later it disappears, but as convalescence begins it reappears and for a time becomes excessive, just as in the preliminary stage, as the result of the meningeal congestion and its predominance over bacterial activity.

In chronic cases the meningococci may lose their power of fermenting dextrose, and the cerebro-spinal fluid, although opalescent and containing meningococci, reduces Fehling, and becomes more alkaline than during the acute stage. The presence or absence of the reducing power of the cerebro-spinal fluid has been utilised as a clinical test for distinguishing the meningism sometimes seen as a manifestation of serum disease in patients who have had intrathecal injections of antimeningococcic serum from a true relapse of the infection, in which event the reducing body is absent (Reveillet, Nové-Josserand, and Langeron [88]).

Microscopical Characters.

In the very early stage there is an increase in the small number of lymphocytes normally present. In some exceptional cases there is a well-marked lymphocytosis at the stage, but, if the patient survive, this is succeeded by the ordinary polymorphonuclear predominance (Dopter). In chronic cases with hydrocephalus in adults and in the posterior basic meningitis of infants, which is a chronic meningococcic meningitis, the cells are mainly lymphocytes. With these exceptions the leucocytes are polymorphonuclears, which at first constitute 95 per cent. or more of the cells; as improvement occurs the number diminishes, and in favourable cases there may, on the fifth day of treatment, be 50 per cent. of polymorphonuclears and 50 per cent. of lymphocytes, and later the eosinophils may increase at the expense of the other leucocytes until almost all the cells are eosinophils (Bloch and Hébert [12]).

In addition to leucocytes the cerebro-spinal fluid contains large mononuclear cells constituting, according to Netter and Debré, 5 to 20 per cent. of the cells; they may be enormous, as large even as 20 to 40 leucocytes, are phagocytic, and are derived from the connective tissue cells and lymph spaces of the pia arachnoid.

The meningococci may be extracellular or intracellular, and their number does not correspond to the clinical symptoms. Gordon's [39] remarks suggest that lysis of the meningococci and liberation of endotoxin may account for the difficulty in finding meningococci in severe cases.

Mixed and Secondary Infections.

In addition to the meningococcus the cerebro-spinal fluid may show various micro-organisms, such as the tubercle bacillus, the pneumococcus, the influenza bacillus, streptococci, and staphylococci. Among 339 cases in the Navy there were 8 of this kind, 4 with streptococci, 3 with pneumococci, and 1 with tubercle bacilli; such cases are, of course, usually fatal, and recovery occurred in one case only, with pneumococcic infection present at the first lumbar puncture.

The commonest secondary infection appears to be pneumococcic; Netter and Salanier [80] met with 22 cases of secondary pneumococcic infection among patients with meningococcic meningitis treated by intrathecal injections of serum during the first four months of 1917, when from the increased incidence of primary pneumococcic meningitis since December, 1916, the virulence of the pneumococcus was presumably intensified. These authors suggest that the injection of serum into the subarachnoid space, especially

when large quantities of serum not corresponding to the type of the meningococcus present are given, may provide a better culture medium and so favour pneumococcic infection. But a mixed meningococcic and pneumococcic infection of the meninges may occur before lumbar puncture, as was found in a naval case ; and it would appear that secondary pneumococcic infection depends mainly on the virulence of the pneumococcus, for in a previous series of 300 cases of meningococcic meningitis Netter and Salanier [81] found four cases only of secondary pneumococcic infection. On the other hand, it must be remembered that horse serum causes an aseptic meningitis and facilitates the passage of micro-organisms from the blood through the meninges. In order to prevent this secondary infection these authors advise the addition to the antimeningococcic serum of antipneumococcic serum. But this would be likely to be effective only if the pneumococcus were Type I. and the corresponding serum, which is the effective one, employed.

Fitzgerald,[31] who reports 12 cases of meningococcic meningitis, three of which were also infected with pneumococci, suggests that this secondary infection is commoner than is usually recognised, and quotes Mervyn Gordon's opinion that it occurs in 5 per cent. of the cases. He points out that unless the lumbar puncture fluid is bacteriologically tested on each occasion cases may easily be missed, and thus the real reason for ascribed failures of serum treatment be undetected. All the reported cases of combined meningococcic and pneumococcic infection, with the exception of three recorded by Netter and Salanier, proved fatal.

Combined *tuberculous* and meningococcic infection of the meninges is very rare. Of the recorded cases Bériel and Durand [10] accept eight only. Sophian has never seen such a combination among 300 cerebro-spinal fluids examined from cases of tuberculous meningitis, and states that no such coincidence has been established in New York. The interesting question arises as to the relation in point of time between these two infections. On general grounds it would appear probable that the more acute meningococcic is implanted on the tuberculous infection (Lutaud [63]), but the opposite view—namely, that meningococcic infection facilitates tuberculosis of the meninges has found supporters. Thus, Sainton,[98] in recording two cases of this double meningitic infection with old tuberculous lesions in the lungs suggests two alternatives: (1) that the meningococcic infection led to transfer of the tubercle bacilli to the meninges ; and (2) that the active meningeal reaction due to intrathecal injections of serum awoke old tuberculous lesions there.

Streptococcic infection may spread from the lumbar puncture wound, be due to otitic infection, or arise without any obvious focus of infection. Mixed infections may occur in cases of ear disease ; thus, Jaffé [54] records a case

of a soldier with chronic otitis in whom after death suppuration of the right lateral sinus and pus at the base of the brain containing meningococci, streptococci, and staphylococci were found. Lüdke [62] mentions cases of bacteriologically proved meningococcic meningitis in which blood cultures, though negative for meningococci, showed streptococci or staphylococci.

Rashes.

The incidence of rashes varies in different epidemics; thus, in one of the earliest accounts of the disease North says that hæmorrhages, which in 1806–07 marked almost every case, were rarely observed in 1808–09. Writing in 1911, Netter and Debré stated that eruptions have been, generally speaking, commoner in Britain and America than in Germany, and especially in France,

In the years before the war rashes were very rare in sporadic cases in adults and were hardly ever seen in children, but during the increased prevalence since 1914 rashes—and at present I am not including herpes—have been common; thus, among 502 cases in the Royal Navy during the first four years of war there were 296, or 59 per cent., with rashes. In France also purpura has become more frequent during the war, and Netter [71] has suggested that this may be correlated with Dopter's observation that whereas before the war the infecting strain of meningococcus was in 96 per cent. of cases Type A (Gordon's I. and III.), during the war, Type B (Gordon's II. and IV.) has become equally if not more important, and that the increased frequency of meningococcæmia is also thus explained. In her thesis on the purpuric forms of meningococcæmia Mlle. Blanchier [11] has brought forward some evidence in favour of this view; out of 10 cases she was able by examination of fluid or blood from the hæmorrhagic areas to determine that in 5 cases the infecting meningococcus belonged to Type B. (Gordon's Types II. and IV.) and in 1 case to Type A (Gordon's I. and III.).

This is, perhaps, the most convenient place to refer to the cases of meningococcic purpura without meningitis. Among 277 cases Netter had 19 of meningococcic purpura without meningitis, and states that it has become commoner and that as bullæ can be raised by friction over the purpuric areas more easily than in other forms, this may be utilised to determine the strain of the infecting organisms and so enable the corresponding serum to be selected. Surgeon-Lieutenant-Commander D. H. C. Given [38] described a series of febrile purpuric cases, many of which I saw, arising in connexion with cases of cerebro-spinal fever in the *Powerful* establishment at Devonport; in only 3 of these could meningococci be cultivated and none of them could be

identified with Gordon's types. Meningococcic purpura may be associated with pain in the joints and synovitis.

Varieties of Rashes.

The cutaneous rashes accompany or closely follow the onset of the disease. They appear on the first or second day of the disease and are comparable to the rose spots of enteric fever. There is almost always an interval of two to three days between the appearance of the initial rash and of labial herpes in cases which show both.

The characteristic rash is hæmorrhagic, and may be either small and petechial, resembling that in malignant endocarditis, or purpuric like that in the malignant forms of the exanthemata and acute lymphocytic leukæmia. Sir William Osler has told me of an Oxford undergraduate who died within 24 hours of fulminating septicæmic cerebro-spinal fever; microscopically Dr. A. G. Gibson found the blood-vessels of the skin crowded with meningococci. The prognostic significance of the petechiæ and the large purpuric areas differ; the large purpuric areas are characteristic of the fulminating cases, whereas the petechiæ are not of grave omen. The rash may be petechial or purpuric from the start, or the petechial character may supervene on an erythematous, papular, rose-spot, macular, or blotchy eruption. According to Herrick the large purpuric areas are independent of, and do not spread from, the petechiæ. The non-hæmorrhagic rash may not undergo any further change. In one naval case the rash almost disappeared directly after lumbar puncture. Among 339 naval cases during the second, third, and fourth years of the war there were hæmorrhagic rashes in 153 and non-hæmorrhagic in 42. The erythematous rash has been described as transient and is seldom recorded. Occasionally the initial rash is described as urticarial.

The rose spots, papules, and petechiæ are presumably embolic and evidence of the stage of septicæmia or blood invasion. They are more prone to occur in parts exposed to friction, especially the joints; in some instances the hæmorrhagic eruption may be partly vesicular, in others bullæ may form over purpuric areas, and in one such case in the Navy a pure culture of meningococci was obtained from the fluid. In rare instances ulceration may supervene in large hæmorrhagic areas, and yet recovery follow (Gordon,[40] Bovaird,[13] Robb,[89] Elliott and Kaye,[26] and a naval case). Trophic bullæ may form on various parts of the body, such as the fingers, and, according to Fairley and Stewart,[28] are sterile. These observers divide the rashes into (1) primary—namely, the purpuric, petechial, and macular, due to septicæmia; and (2) the secondary, which do not appear until after the third day of the disease and are regarded as toxic. Of the latter class they describe the "elbow sign," which

consists of a flush on the extensor surface of that joint and also above the great trochanter of the femur, generally combined with a condition of "hæmorrhagic goose skin." This description applies to a condition commonly recognised, but regarded as the petechial rash on points of pressure and aggravated by friction. The appearance is well shown in Plates II. and III. of Foster and Gaskell's Monograph in patients dying on the second and fourth days of the disease. Fairley and Stewart contest its relation to pressure.

Herpes.

Herpes is a well-recognised event in cerebro-spinal fever and may be considered under the two heads of (1) ordinary febrile herpes labialis; and (2) herpes of the zoster type.

Herpes labialis appears to occur with varying frequency in different epidemics, and the relative incidence of herpes labialis and of other cutaneous eruptions shows similar fluctuations; from a review of the literature up to 1898, Councilman, Mallory, and Wright[21] concluded that herpes is far commoner than any other eruption. Netter[74] found that herpes occurred in a third of his cases and was more frequent than purpura, and Sainton[98] states that it was present in two-thirds of his cases. High estimates were also given by Leichtenstern (90 per cent.), Leyden (75 per cent.), Tourdes (60 per cent.), and Friis (54 per cent.). On the other hand, Stillé[104] says that in the Massachusetts epidemic herpes was infrequent and much less often present than cutaneous rashes; in 502 naval cases there were 117, or 23 per cent., with herpes and 296, or 59 per cent., with rashes. As herpes labialis ordinarily is prone to occur again and again in certain persons, it is possible that its incidence in cerebro-spinal fever is to some extent determined by personal idiosyncrasy. Out of the 117 cases of herpes in the Navy, 96, or 82 per cent., had in addition an initial rash (54), a serum rash (31), or both (11).

Labial herpes appears later than the initial rash and usually on the fourth day of the disease, but it may occur earlier, on the second day, or be postponed until later; in two naval cases it came out with the serum rash on the eighth and tenth days of the disease, and may then be regarded as part of the serum disease rather than of cerebro-spinal fever. In rare instances it may recur during continued fever, with a recrudescence of symptoms, or with the appearance of some complication. It is unusual in children and exceptional in infants; among Robertson's[92] 66 cases under 16 years of age it did not occur, but it was noted in four out of 33 children under 4 years of age reported by Mitchell and Falkener,[69] and in 15 out of 48 children and in two out of 21 infants collected by Collette;[18] among the

naval cases which range from 15 years upwards age did not exert any obvious influence.

The causation of ordinary herpes labialis is undecided; it is not generally thought to be associated with any lesion of the central nervous system, though Howard,[49] from histological examination of the Gasserian and other ganglia, considers that the herpes of pneumonia and cerebro-spinal fever has a similar anatomical basis to that of herpes zoster. Though frequently looked for, meningococci have very seldom been isolated from the vesicles of labial herpes (Durand, von Drigalski), but Durand[24] argues that the meningococci may be overgrown by secondary infections. Clinically the appearance of herpes on the fourth day of the disease, some days after the initial rash which is presumably due to emboli of meningococci, militates against the view that these two eruptions are due to the same mechanism. It has, however, been suggested that the vesicles are due to meningococci, and their situation determined by inflammation of the Gasserian ganglion. As herpes labialis has been seen in persons reacting vigorously to prophylactic antimeningococcic vaccines (Gates[37]) it appears to me reasonable to refer it to the local action of toxins rather than of bacteria in the skin. The vesicles commonly occur on both lips and may extend out on to the cheeks and nose (facial herpes), so that sometimes it is difficult to determine where labial herpes and herpes due to implication of the fifth nerve begin and end.

Herpes of the zoster type occurs in cerebro-spinal fever, but much less often than labial herpes. The two forms may be present at the same time; thus labial herpes and herpes of the external ear due to inflammation of the geniculate ganglion of the facial nerve (Ramsay Hunt[50]), or labial herpes and herpes of the neck may be combined. Herpes of the face due to inflammation of the Gasserian ganglion of the trigeminal may be very profuse, or single branches may be picked out; I have seen nasal herpes without ulceration of the cornea; Ballantyne[5] describes herpes of both eyelids on one side. Herpes of the limbs is rare; Robb[90] refers to cases, Netter and Debré[77] figure bilateral herpes on the backs of the thighs, and Sainton describes a case with supra- and infra-orbital herpes and a few vesicles on the dorsum of the hand. It would be interesting to have figures to show the date of the appearance of herpes zoster; my impression is that it occurs earlier than the labial form.

Nervous Symptoms.

Nervous symptoms are predominant at the onset of meningitis; severe headache, vomiting, and mental stupor or delirium are usually present and there may be wild mania,

symptoms suggesting delirium tremens, or epileptic seizures. The mental disturbances during the septicæmic stages, and before meningeal infection has occurred, are probably toxic and comparable to those at the commencement of other acute infections, such as pneumonia. Incontinence of urine and fæces is common. Swallowing may be difficult, either from œsophageal spasm or paresis, and is probably more frequent than the notes of cases show. Among the 502 naval cases it was mentioned in 8 (5 fatal). In a case recorded by McConnell, Morris, and Seehorn [64] œsophageal spasm was so obstinate that gastrostomy was done, death following 12 hours later. General hyperæsthesia is not uncommon.

The condition of the *reflexes* varies; the deep reflexes are often exaggerated and an extensor response may be present; among 398 naval cases Babinski's sign was noted in 35, or 8 8 per cent.; it may be obtained on one side only. Herrick [44] insists that whereas in other acute infections the deep reflexes may be equally exaggerated on the two sides, in cerebro-spinal fever there is a notable inequality. It is stated that in the most severe cases both the superficial and deep reflexes may be abolished, but it is doubtful if any stress can be laid on this; among 21 naval cases in which the knee-jerks were noted to be absent there were 8 deaths. It may be mentioned that the knee-jerks are often absent in pneumonia and may be exaggerated or absent in enteric fever. Kernig's sign and rigidity of the neck are practically constant when meningitis has appeared, and are so well known that they will not be further discussed here.

Facial paralysis is rare; it appears early and is transient. Among 502 naval cases it was recorded in 7, but among Robb's 230 cases there were 11 examples. *Aphasia*, probably due to local pressure from exudation, may occur. Among 502 naval cases it was recorded in 5, in 2 of which it was transient; the other cases were fatal. Among Robb's cases there were 3 of aphasia.

Paraplegia.

Paraplegia is rare; among 502 naval cases it was noted in 1; among more than 400 cases MacLagan found it in 3, 2 of which recovered; there was one example among Robb's 230 cases and none among 120 cases that recovered and were analysed by Worster-Drought.[111] It may be either organic or in very rarely recognised instances functional.

Organic paraplegia is described by Sophian [102] as either (1) spastic with ataxia, clonus, extensor plantar response, no sensory changes, and no vesical disorder; or (2) flaccid with absence of reflexes and sensory changes. Of the

spastic form Sophian has seen 12 cases, presumably due to the pressure of exudate around the cord some way above the cauda equina. The general experience is that the paraplegia slowly improves, and this is in favour of the view that most of the cases are due to the pressure of exudate and not to extensive matting of adhesions and invasion of the substance of the cord by inflammatory products (meningo-myelitis). But sometimes the paraplegia is permanent, and this condition would be expected to be due to lesions of another kind. Thus Carnegie Dickson [23] found extensive softening of the cord, usually in the upper dorsal or lower cervical region. In chronic distension of the ventricles rigid paraplegia may be met with. Foster and Gaskell mention two cases resembling disseminated sclerosis. Flaccid paraplegia may apparently be due to matting of the cauda equina in a mass of adhesions. Herrick [45] describes a case with hæmorrhagic purulent exudate—a condition resembling the radiculitis responsible for flaccid monoplegias.

Functional paraplegia.—In convalescents the gait is naturally at first impaired, and as the patients may be unduly susceptible to auto-suggestion hysterical paraplegia may result. Hurst [51] records such a case in which a soldier, finding that in the early stages of convalescence walking was painful, gave up the attempt. The central nervous system was free from organic disease, and a rapid cure was effected by vigorous persuasion.

Hemiplegia.—Monoplegias.—Nerve Deafness.

Hemiplegia is rare and, like paraplegia, may be organic or functional. Among the 502 naval cases it occurred in 12, 10 of which proved fatal. Robb found 4 cases of hemiplegia among 230 cases at Belfast. In fatal cases cerebral softening, compression of the cortex by masses of exudation, and cerebral hæmorrhage have been reported. The hemiplegia comes on during the acute disease and may appear a few days before death; if the patient recovers it may be permanent, but the tendency to improve in many patients who survive suggests that more of the reported hemiplegias may be functional than is realised. Beaussart [8] reports a case of cerebro-spinal fever in February, 1917, with functional hemiplegia the following July.

Monoplegias of the limbs due to inflammation of the nerve roots (radiculitis) as they pass through the meninges are described by Netter and Debré. They are even rarer than hemiplegia, occur earlier, are accompanied by wasting, pain, loss of reflexes and of sensation, but they usually disappear. Some only of the muscles of the limb may be affected. Sophian, however, states that monoplegias occur late in the

course of the disease. These flaccid monoplegias must be differentiated from those due to acute poliomyelitis, which have not the same tendency to recover.

Nerve deafness is not nearly so common now as it appears to have been formerly.

Thus, according to Hutt,[52] among 874 pupils in the London County Council schools for deaf children requiring tuition only 1 was due to cerebro-spinal fever. Among 502 Naval cases deafness occurred in 26; it is usually regarded as due to extension of inflammation from the meninges along the sheath of the auditory nerve and is permanent, but in 2 cases temporary deafness about the time of the serum rash was regarded by Temporary Surgeon-Lieutenant A. C. MacAllister as a toxic manifestation of serum disease.

Deafness may also be due to otitis media, which is not regarded as a common complication of cerebro-spinal fever; among 502 naval cases it was noted in 10. But some writers state that a mild form of otitis media is very common.

Ocular Signs and Symptoms.

The *pupils* are usually dilated, due to irritation of the sympathetic, and when sluggish in addition point to increased intracranial pressure. The pupils may diminish in size and regain their activity after lumbar puncture and relief of pressure, and dilate when an attempt is made to straighten the head or to obtain Kernig's sign. In some acute cases the pupils are much contracted. Inequality of the pupils is fairly frequent, especially in bad cases; hippus is common but without any special significance.

Photophobia, said to be rare and thus to contrast with its frequency in tuberculous meningitis, was reported in 52, or 10 per cent., out of 502 naval cases, and was almost always an initial symptom. Among 73 cases specially examined Ballantyne[5] never found true photophobia, though spasm of the eyelids, usually associated with general hyperæsthesia, was very frequent, and he considers that this has probably been described as photophobia.

Conjunctivitis is not very common; it occurred in 5·6 per cent. of 502 naval cases, in 10, or 9 per cent., of Councilman, Mallory, and Wright's[21] 111 cases, in 15, or 20 per cent., of Ballantyne's 73 cases, and in 20 per cent. of Fairley and Stewart's series. The pus may, but does not always, contain meningococci. According to Councilman, Mallory, and Wright suppurative conjunctivitis may be due to loss of sensation depending on destruction of the Gasserian ganglion. When occurring early in the course of the disease, as it

commonly does about the second day, it is usually of little importance, but when it appears later it may be followed by panophthalmitis. A certain degree of conjunctival engorgement in association with vaso-dilatation of the face is common. Conjunctival hæmorrhages are sometimes present, and are important diagnostically, as they are practically never seen in other forms of meningitis. Among 339 naval cases conjunctival hæmorrhages were noted six times. Corneal ulcer may occur and show the meningococcus. The analogy of gonococcic arthritis in the newly-born, which may be secondary to conjunctival infection, is possibly paralleled by Miller's [68] case of an infant who when two weeks old had conjunctivitis followed in two weeks' time by meningitis.

Panophthalmitis is rare and is commonly unilateral; Levy [61] (of Essen) had the exceptional experience of seeing 9 cases, 8 unilateral, among 165 cases of the disease. Among the 502 naval cases it occurred in 7, or 1·4 per cent., and was bilateral in 2 and unilateral in 5, all on the right side; in this connexion attention may be drawn to Netter's suggestion that the position of the patient's head, on the right or left, determines the side on which unilateral panophthalmitis occurs. As long ago as 1867 Gordon [40] noticed the predominance of these infective conditions in the right eye. Councilman, Mallory, and Wright insist that, contrary to the firm belief of most ophthalmologists, panophthalmitis is not metastatic, but is due to direct extension of inflammation around the optic nerve and arteria centralis retinæ and give a figure in support of their contention. Herrick insists that the infection travels by the ciliary vessels and not by the sheath of the optic nerve. Panophthalmitis may begin at different dates; Netter and Debré mention the twelfth to the fifteenth day of the disease, but in two naval cases it began on the fourth and the eighth.

Suppuration in the orbit, a very rare complication, is regarded by Councilman, Mallory, and Wright as due to extension from the meninges, whereas Netter and Debré consider that the inflammation spreads from the accessory nasal sinuses.

Optic Neuritis and Other Nerve Lesions.

Optic neuritis is usually regarded as infrequent and thus contrasting with its incidence in tuberculous meningitis; among 389 cases obtained by adding together the series reported by Ballantyne, Randolph, Travers Smith, Foster and Cooke, Uhthoff, and Heine, 39, or 10 per cent., had optic neuritis. On the other hand, Fairley and Stewart [28] report the result of a routine bi-weekly examination by Dr.

Gault of 184 cases; of these, 116, or 63 per cent., had optic neuritis, and of these 78, or 67 per cent., had a rash, whereas of 68 cases without optic neuritis 32, or 47 per cent., had a rash, the conclusion being drawn that optic neuritis is specially related to septicæmia. In cases with internal hydrocephalus optic neuritis was almost always absent, and this is explained on the ground that when internal hydrocephalus is absolute there is no fluid in the subarachnoid space to distend the vaginal sheath of the optic nerve.

True *nystagmus* occurs in severe cases only, and by Fairley and Stewart is regarded as pathognomonic of internal hydrocephalus, and therefore of extremely grave prognosis. It must be distinguished from pseudo-nystagmus or jerky movements at the limit of fixation, which, according to Ballantyne, are without significance.

Strabismus, usually due to implication of the sixth nerve, is much less frequent than in tuberculous meningitis, and is usually transient. Ballantyne found that the squint was nearly always (14 out of 15 cases) spasmodic, and thus contrasted with the squints in tuberculous meningitis, which are much more commonly paralytic. Among 502 naval cases squints were noted in 59 cases, or 11·7 per cent.; among Robb's 230 cases in 28 per cent.; among Councilman, Mallory, and Wright's 111 cases in 25·3 per cent.; and in Ballantyne's 73 cases in 25·5 per cent. Among the 59 naval cases with strabismus 31, or 52·5 per cent., proved fatal. Strabismus is an early symptom, usually within the first week of the disease, whereas in tuberculous meningitis, strabismus is a late event.

Ptosis is much less frequent than strabismus; out of the 502 naval cases it was noted in 18, or 3·6 per cent., but 13, or 72 per cent., of these 18 cases terminated fatally. The mortality was thus 20 per cent. higher than in the squint cases; this may be correlated with the probable spasmodic nature of many of the squints and the paralytic origin of the ptoses.

Retraction of the upper eyelids may occur; among 73 cases Ballantyne noted it in 15, one of which also showed von Gräfe's sign. According to Batten [7] it is common as an early manifestation in posterior basic meningitis before hydrocephalus, of which it is a recognised result, has developed. It varies in degree and is exactly like that due to stimulation of the sympathetic, but is not necessarily associated with dilatation of the pupils.

Circulatory Symptoms and Complications.

Pericarditis is probably often latent, as it is found after death when previously unsuspected—an experience familiar in other conditions. Netter and Debré speak of pericarditis as a phenomenon almost confined to the post-mortem table, and some authors do not refer to it. Robb,[90] however, noted pericardial friction in 17, or 7·4 per cent., out of 230 cases, Herrick[45] refers to 11 cases among 265, and it was heard in 4 naval cases that recovered. Extensive pericardial effusion is rare, and it appears that the pericarditis is usually dry and fibrinous. In a case of Herrick's[44] 110 c.cm. of blood-stained purulent fluid, giving a pure culture of meningococci, were removed, and 30 c.cm. of serum injected into the pericardium with benefit. As subpericardial hæmorrhages are common after death in fulminating cases pericarditis of meningococcic origin is easily explained. In 1908 Duval[25] collected 5 cases of bacteriologically proved meningococcic pericarditis.

Endocarditis is probably not so rare as it has been stated to be, but the vegetations may be small and possibly are sometimes overlooked. Among Ivy Mackenzie and Martin's[65] 20 cases 2 had malignant endocarditis, and Krumbhaar and Cloud,[56] among 16 cases of cerebro-spinal fever, found 3 with acute vegetative endocarditis. Cases of meningococcic endocarditis without meningitis are much rarer and are referred to elsewhere. Cardiac murmurs, commonly at the apex and referable to muscular incompetence, are not infrequent. Among 339 naval cases this was noted in 16 (1 death). Permanent valvular lesions, though they might be expected from the occurrence of meningococcic endocarditis, must be very rare.

Phlebitis in the lower extremities has been reported in rare instances. Collette[18] describes the association with arthritis in a girl aged 2½ years.

The blood shows a polymorphonuclear leucocytosis of from 20,000 to 50,000, and, according to Koplik,[55] is over 25,000 in more than half the cases ; in chronic cases the leucocytosis may fall to normal.

Pulse and Blood Pressure.

The pulse is usually regular though it may, especially in grave cases, be irregular. Like the temperature the pulse-rate may vary greatly within a short time. The outstanding feature about the pulse is that it is so often slow in relation to the temperature ; thus in a naval chaplain who was

maniacal in the early stage the temperature was 105° F. and the pulse 60. The slow pulse depends on vagal inhibition due to increased intracranial pressure. Sainton[98] states that in the early stage of the disease pressure on the eyelids does not modify the pulse, but that later and at the height of the disease this oculo-cardiac reflex is always positive, the pulse becoming slowed by 16 to 50 beats per minute, and that this shows that the usual slow pulse in cerebro-spinal fever is due to vagotonia. In fulminating and septicæmic cases the pulse is rapid, as in most other acute infections. In fulminating cases the pulse may become impalpable some time before death. In some cases the pulse is rapid during convalescence, probably from toxic changes involving either the myocardium or the nervous mechanism of the heart. This rapid pulse is sometimes seen in patients who have got up soon after the illness. Before death the pulse may become extremely rapid.

The arterial blood pressure, which has been specially studied by Sophian and more recently by Fairley and Stewart, is low in the septicæmic stage, and in the worst cases may be impossible to record, rises with the increased intracranial pressure accompanying the onset of meningitis, and may then be between 140 and 190 mm. Hg, and in internal hydrocephalus is almost always raised from pressure of the cerebro-spinal fluid on the floor of the fourth ventricle. During convalescence the blood pressure is, in the absence of complications, normal or subnormal. In the acute stage vaso-motor disturbance is often extremely well marked, the face is intensely and characteristically congested—more so than in most fevers. This may, perhaps, be correlated with the changes commonly found in the medulla of the adrenals. The *tache cérébrale* is usually well marked, but is not of any diagnostic value. Epistaxis is occasionally seen.

Temperature.

The temperature is very irregular and does not conform to any rule; probably every case has fever at some time during the course of the disease, but some charts show little or no elevation of the temperature. This may be because the temperature varies rapidly and it so happens that when it is taken it is not up. In cases with a very severe onset the temperature is often at first depressed from collapse and then rises so that hyperpyrexia may occur. A low temperature is said to be characteristic of the disease in elderly people. There may be extreme oscillations at very short intervals—a feature of some diagnostic value in the early stages according to Netter. In chronic septicæmia the temperature chart may imitate that of malaria or enteric, and in chronic loculated meningitis there may be irregular

bouts of fever which in posterior basic meningitis have been described as crises due to increased intracranial pressure. In some acute cases there is agonal hyperpyrexia, in others a low temperature.

Pulmonary Complications.

Pulmonary complications in this country since the war have not been very common; bronchitis and broncho-pneumonia have been the most frequent and important. Bronchitis as a complication is dangerous and cases in which it appears after some days' illness with meningitis usually prove fatal. An initial bronchitis does not necessarily make the prognosis so grave. Pneumonia has been seen in some cases and it is known that pure meningococcic, as well as pneumococcic, pneumonia may complicate meningococcic meningitis and even occur without meningeal infection (Jacobitz [53]). Pneumonia may be present at the onset or appear later in the course of the disease.

Pleurisy may, of course, accompany pneumonia or broncho-pneumonia in the course of cerebro-spinal fever, but it may occur without any obvious lung lesion; this was noted in 3 out of 502 naval cases. Meningococcic pleurisy has been recorded by Herrick, but it may be due to other organisms; thus, Krumbhaar and Cloud mention a case with acute staphylococcic pleurisy. Netter and Debré refer to a bilateral hæmothorax in a child with a purpuric eruption. In the past pulmonary complications have from time to time been prominent features in individual outbreaks, and recently Herrick found them not uncommon among 208 cases.

Complications Involving the Alimentary Canal.

Parotitis is rare; it may be due to an ascending infection from the mouth, as in other fevers and conditions in which the mouth is dry. It may be unilateral and be associated with suppuration in the neck or otitis, or be non-suppurative. In the pus of one of Fairley and Stewart's cases *Staphylococcus aureus* was found. But in a suppurative case Robb reported the presence of the meningococcus, and as this organism does not flourish in the saliva the infection may have been hæmic.

In the most severe cases there may be blood in the vomit and fæces, but rarely in considerable quantities. Diarrhœa is not uncommon as an initial symptom and, as mentioned elsewhere, abdominal symptoms may be so prominent as to suggest an acute perforation of the alimentary tract, appendicitis, or Henoch's purpura. Jaundice is quite exceptional, and one case of peritonitis is tabulated by Herrick.

Lesions of Joints.

Arthralgia, or pain in the joints like that of influenza, is common at the onset and in the early stage of the disease, but is often overshadowed by the more severe symptoms. It may, however, be the precursor of synovitis and then is presumably similar in nature. It may accompany a hæmorrhagic eruption on the skin, and is very probably due to meningococcic emboli and hæmorrhages in the synovial membranes of the joints.

Arthritis, or more often synovitis, is a recognised complication of cerebro-spinal fever, and may occur in meningococcic infection without meningitis; four cases of this nature have been reported by Cecil and Soper,[16] three by Sainton,[98] and two by Faroy and May[29]; it has been recorded in meningococcic purpura (Given[38]), and in such cases has sometimes been regarded as "peliosis rheumatica." It is due to meningococci carried to the joints by the blood stream, and may therefore be associated with other metastatic manifestations, such as irido-cyclitis, epididymitis and orchitis. In cases of meningitis with synovitis it is often found that there was an initial hæmorrhagic rash; this was so in 15 out of 16 naval cases in which the point was investigated. It usually occurs on the fourth, fifth, or sixth day of the disease, but it may precede other symptoms.

The incidence was estimated at from 10 to 15 per cent. by Sophian and from 5 to 20 per cent. by Roger,[94] but among 502 cases in the Navy it occurred in 24, or 4·8 per cent., and among Fairley and Stewart's 323 cases in 23, or 7 per cent. Among 902 other cases (Robb's, Herrick's, Netter and Durand's,[78] Sainton's, Lafosse's,[58] and some others) there were 59 cases of synovitis, or 6·5 per cent. It is more often seen in adolescents and adults than in babies, thus recalling the incidence of synovitis in acute rheumatism; but when it does occur in babies the hands and feet are specially picked out, whereas in older patients the larger joints—the knees, wrists, and ankles—are usually attacked. In posterior basic meningitis Still[103] found peri-articular infection, the joint cavities being healthy, in 4 out of 49 cases examined after death, and Osler,[82] in his Cavendish lecture, said the lesions were generally peri-articular.

The joint tissues are little affected, and though suppurative synovitis with characteristic grass-green pus occurs, it must be rare; only one out of the 24 naval cases required aspiration, the affection being usually of short duration, as if a serous synovitis, though two cases lasted for six weeks and showed relapses. According to Netter and Durand the pus in the early cases shows meningococci, which may die out in the chronic cases. Horder refers to a case with meningococci and *Staphylococcus aureus* in the pus.

Clinical Features of Joint Lesions: Prognosis.

The accounts of the clinical features of the joint lesions in cerebro-spinal fever vary; thus, by some writers the joints are said to be very painful, by others as tolerant of movement. This is probably to some extent explained by adopting Herrick's [44] description of two groups of cases: (*a*) the early synovitis occurring in the septicæmic stage, and sometimes before the appearance of any meningitic symptoms; several joints are attacked, usually are very painful though but slightly swollen, show local heat, some redness or erythema of the skin, and even a rash. Sometimes the existence of these effusions is latent; thus, an effusion into the knee may be only discovered on trying Kernig's sign. The condition closely resembles that of acute rheumatism, and I have seen it accompanied by acute pericarditis. These cases of early synovitis are the commonest, and most of the 24 naval cases belonged to this category. (*b*) The late cases of arthritis which are monarticular, the knee usually being attacked, purulent, with much local swelling, little redness of the skin, relatively little pain, freedom from muscular spasm, and little limitation of movement, there being a remarkable contrast between the considerable degree of swelling and the slight functional impairment.

The prognosis as regards the condition of the joint is good; the early cases clear up rapidly and commonly without any necessity for the intra-articular injection of serum. Even suppurative cases may clear up after simple aspiration. Ankylosis, of which Roger records a case with implication of the hip and knee, is rare. Other cases have been reported by Netter and Josias,[79] and Sainton and Bouquet,[101] who report a case with arthritis of the shoulder, subsequently becoming ankylosed before the onset of meningitis and later suppurative arthritis of the knee after the meningitis. According to Netter [72] cases with articular lesions usually do well, with the exception that in infants the mortality is high; but, as pointed out elsewhere, the mortality in infants is usually high because the treatment is commonly begun so late. Among 24 naval cases there were six deaths, or 25 per cent., a lower rate than that (41 per cent.) among the 502 cases.

The chronic cases of meningococcic pyarthrosis may imitate gonococcic or tuberculous arthritis. When the synovitis occurs about the eighth day of the disease it may be difficult to decide whether it is meningococcic or the first sign of serum disease. For the treatment intra-articular injection of serum has been widely recommended, but most cases clear up with purely symptomatic treatment. Salicylates do not exert any influence on the synovitis, but aspirin relieves the pain.

Urinary Changes.

The urinary changes are not characteristic or of clinical importance.

Cystitis may occur, and the incidence of pyuria has varied in different outbreaks ; Fairley and Stewart's percentage of 40 is much the highest I have come across. *Pyelitis* was reported in 5 per cent. of the Texas epidemic by Sophian, who described meningococci in the urine ; but general experience shows that meningococci are rare in the urine, and that cystitis and pyuria during the disease may be due to other organisms ; in this connexion it may be mentioned that the changes in the lymphatic tissue of the alimentary canal have been thought to favour hæmic infection of the urinary tract with *Bacillus coli*. *Polyuria* is occasionally noted ; it is stated to be a critical phenomenon, but it may certainly occur while the temperature remains high.

Albuminuria is not very common, and when present is usually small in amount. Cazamian [15] is exceptional in finding it in all his 113 cases, but in many it was transient or in traces only. It is commonest early in grave cases, but otherwise it has no prognostic significance, and permanent renal change never follows. Albuminuria is rarely accompanied by casts, and is regarded by Cazamian as not renal, but due to changes in the medulla oblongata. Occasionally transient albuminuria occurs synchronously with œdema and urticaria—"serous hæmorrhages"—of serum disease.

Hæmaturia is not common ; when it occurs it usually is an early complication, and is associated with a petechial or hæmorrhagic rash ; it is presumably caused by hæmorrhages in the mucous membrane of the urinary tract, but is not so often seen in the fulminating cases with much purpura as might naturally be expected. Among the 502 naval cases it was noted in 4 only ; in 3 of these it was associated with a petechial rash ; in the other it was due to an acute ascending pyelitis. Among Neave's 73 cases two had hæmaturia. If the patient be taking hexamine this may be the explanation.

Glycosuria is rare and may be quite transient. Among Cazamian's 113 cases it occurred in 9, or 7·9 per cent., but acetone bodies were never present. There was one case only among Sophian's series. It may occur at the onset, and when found in an unconscious patient has been thought to indicate diabetic coma. It may be associated with albuminuria ; Flack [32] mentions a case of nephritis with blood and sugar in the urine, which recovered rapidly. In a naval case that recovered albuminuria, glycosuria, and

acetone in the breath were noted on the second day of the disease. It is stated to be less frequent than in tuberculous meningitis, in which it occurs late; Garrod and Frew [36] found it in 15 out of 41 cases of tuberculous meningitis but never in posterior basic meningitis. The glycosuria would appear to be nervous and central in origin, but more than this it is difficult to say. It is not due to increased intracranial pressure or to hyperpituitarism which diminishes the sugar tolerance, for examination of the gland does not reveal any changes different from those in pneumonia, and some observations made by Fairley and Stewart showed that the behaviour of the sugar tolerance and of the blood pressure in cerebro-spinal fever do not lend any support to the view that peri-hypophyseal inflammation by causing increased vascularity induces increased functional activity of the gland.

Urobilinogenuria was recorded by Cazamian in three-quarters of his 113 cases; it was most intense at the onset and was as frequent in the non-septicæmic as in the septicæmic cases. *Indicanuria* is stated to occur in grave cases (Netter and Debré), but was detected by Cazamian in two only out of his 25 fatal cases.

Epididymitis and Orchitis.

Epididymitis or orchitis are complications of cerebro-spinal fever, and the meningococcus has been obtained by puncture of the inflamed organ (Florand and Fiessinger [34]), but the text-books rarely mention the lesion. Like other complications, the incidence varies; it is said to have been specially frequent in the Silesian epidemic; among the 290 cases at Camp Jackson in 1918 it occurred in 3 per cent., but in a sporadic outbreak of 36 cases at the same camp in October, 1918, more than a third had epididymitis (Latham [60]). Among 502 naval cases it was noted in 13, or 2·6 per cent.; among Herrick's [45] 208 cases at Camp Jackson in 9, or 4·3 per cent.; among Sainton's [98] 64 cases in 3, or 4·7 per cent.; and among McConnell, Morris, and Seehorn's [64] 30 cases in 2, or 6·7 per cent. In all these cases (36, or 3·9 per cent., out of 922) the possibility of gonococcic origin was, of course, excluded.

It appears that both meningococci (Gordon's Types I. and III.) and para-meningococci (Gordon's Types II. and IV.) may be associated with orchitis and epididymitis; but it is interesting that Latham's cases were associated with Type IV., which seems particularly prone to cause septicæmic and metastatic lesions, and is said to be the closest to the gonococcus biologically and culturally. Eschbach and Lacaze's [27] two cases of simultaneous synovitis and epididy-

mitis recall the morphological resemblance between the meningococcus and the gonococcus.

A curious sequence of events is recorded by Beaussart[9] in a man who had cerebro-spinal fever with double orchi-epididymitis in 1917, and in the following year had influenza with a recurrence starting in the testis and spreading to the epididymis.

In some instances puncture of the inflamed organ has failed to give meningococci, and Latham, whose cases all received massive intravenous injections of serum, found that epididymitis was not a sequel of serum injections in pneumonia ; in some of the naval cases the onset coincided with a serum rash. These data raise but do not settle the question whether some of the cases may be infective, others toxic or anaphylactic. In Latham's cases 70 per cent. had given a positive blood culture, and though none of them had a relapse after the appearance of the epididymitis he inclines to the view that the lesion is septicæmic.

The recorded descriptions refer both to epididymitis and orchitis, and some authors have recorded cases in which the epididymis and body of the testis were affected successively (Florand and Fiessinger, Sainton). In Latham's cases the epididymis alone was inflamed, in McConnell, Morris, and Seehorn's 2 cases the testis exclusively. Probably the epididymis is more often attacked. There does not appear to be any good reason to believe that orchitis and epididymitis are due to different mechanisms ; it might be thought that epididymitis is due to an ascending infection from the bladder, late in the course of the disease ; but evidence of meningococci in the urine in such cases is very scanty ; thus in three cases of epididymitis on the 46th, 23rd, and 15th days of the disease, recorded by Lancelin,[59] the meningococcus was found in the urine in one only.

As already mentioned, it is generally considered that the epididymitis and orchitis are septicæmic in origin, and it might be thought that this applies particularly to orchitis, and that the incidence would usually be early in the disease. In six cases of orchitis in the Navy the complication, which was bilateral in three cases, appeared on the sixth, eighth, tenth, eleventh, and twelfth days of the disease. In a case of Florand and Fiessinger the right testis became inflamed on the thirteenth day and the epididymis the next day. It is possible that epididymitis or orchitis may, like meningococcic arthritis, precede the onset of meningitis. This is suggested by the history of a private in the Marines who had pain in one epididymis without any evidence of gonorrhœa for three days, and three days later had meningitic symptoms and died four days later from the disease. I have not any reference to cases in boys under the age of puberty.

There may be orchitis alone or epididymitis only, or one may precede the other ; in about 10 per cent. of the cases

the lesion is bilateral. Epididymitis begins in the globus major, and subsequently there may be some effusion into the tunica vaginalis. Orchitis or epididymitis is almost always transient, subsiding without suppuration and not being followed by atrophy. Pick,[85] however, recorded suppuration in both vesiculæ seminales due to the meningococcus. There is not any relation between the incidence of epididymitis and orchitis on the one hand, and the clinical severity of the cases on the other hand.

Relapses and Recrudescences.

There is some confusion between these two terms and therefore some uncertainty about the frequency of true relapses.

Recrudescences, sometimes called intermittent relapses, or the return of symptoms before the patient has really recovered from the disease, are very common and a patient may have several; among the naval cases one patient had 7, and Ker quotes 13 recrudescences. They may be due to reinfection from the throat or from some focus untouched by the intrathecal injections of serum, but what often appear to be recrudescences are really manifestations of encysted meningitis or infection of the cerebral ventricles, the foramina of which are obstructed.

True relapses are rare. Netter[73] appears to draw the line between recrudescences and relapses at a month from the disappearance of symptoms, and reported 4, or 1·6 per cent., among 255 cases. Herrick observed two relapses four and three weeks respectively after convalescence among 208 cases. Sophian, however, estimated that relapses after complete recovery from the original attack occurred in 5 per cent. of his cases. Relapses are, like recrudescences, due to reinfection; in isolated instances they have followed anti-typhoid inoculation (Sainton,[99] Massary and Tockmann[67]) or an attack of enteric fever (Labbé[57]) or measles (Netter). The introduction of serum treatment was at first followed by an increased incidence of relapses, but this is ascribed to failures in the application of the serum treatment. In most cases of a true relapse the symptoms are similar to but milder than in the original attack.

Late relapses at long intervals after the patient has been cured can hardly be distinguished from second attacks. These cases of second attack are very rare; it is noteworthy that one attack of meningococcic infection usually protects against another, and that, as Adami[1] has pointed out, the meningococcus thus differs from the majority of pathogenic micrococci. Councilman, Mallory, and Wright, and more recently Netter, have reviewed the literature on the subject, and refer to North's two cases at 25 and 21 months' interval, Hermann and Kober's at a year's interval, and Warschauner

at five years' interval. A naval rating had bacteriologically proved meningococcic meningitis both in May, 1917, and in February, 1918, and on the occasion of the second attack after 23 days' normal temperature had a relapse with eventual recovery.

Diagnosis.

Bacteriological Examination.

For the certain diagnosis of meningococcic meningitis bacteriological examination of the cerebro-spinal fluid for meningococci is necessary, and similarly in the premeningitic stage of cerebro-spinal fever a blood culture is essential. No doubt genuine cases of cerebro-spinal fever may be ruled out by failure of bacteriological methods to give positive results. But this error is probably much less than that which would result from the inclusion of cases diagnosed on clinical grounds, and in the latter event it would be difficult to know where to draw the line.

Cases with meningitic symptoms and meningococci in the naso-pharynx but not in the cerebro-spinal fluid, though often probably genuine cases, and, indeed, so regarded by Flack,[33] are open to the criticism that they may be meningococcic carriers with meningitis or meningism due to some other cause. Flack's ground for his view was that the meningococcus isolated from the naso-pharynx in three cases in which it could not be grown from the cerebro-spinal fluid was agglutinated by the patient's blood, whereas the other types of meningococci were not. But since then Gates[37] has shown that the blood serum of chronic carriers contains specific agglutinins.

No clinical manifestation is pathognomonic of meningococcic infection. In the presence of an epidemic an acute onset with fever, vomiting, severe headache, and malaise may well arouse suspicion, but a similar train of symptoms may occur in many toxæmic conditions, and together with cerebral symptoms (meningism) may accompany acute infections such as influenza, pneumonia, enteric fever, otitis, malaria. A hæmorrhagic rash, though highly suggestive of meningococcæmia, may be present in pneumococcic, streptococcic, and influenzal infections, and in malignant forms of the exanthemata such as small-pox. From other forms of meningitis, such as tuberculous, pneumococcic, otitic, influenzal, an undoubted diagnosis can be made only by lumbar puncture and examination of the cerebro-spinal fluid.

Lumbar Puncture.

As lumbar puncture is such an essential element in the diagnosis, it is well to insist that the risk of any harm from diagnostic puncture, provided the fluid is not withdrawn too rapidly or in excessive quantities, is almost negligible; some hæmorrhage may occur, but this seldom causes serious damage. In one instance, however, in a case of tuberculous meningitis, lumbar puncture was followed by a bullous eruption on one foot, and after death a clot of blood was found inside the theca vertebralis and in contact with the posterior nerve roots.[95] The cauda equina may be injured and severe pain in the lower limbs thus caused, and I have heard of a case of traumatic aneurysm of a small artery on the posterior surface of the cauda equina as the result of lumbar puncture. In a few instances pain and wasting have followed in a lower limb, suggesting damage to the lumbo-sacral plexus, and it must be admitted that signs of caudal myelitis and even widespread suppuration around the vertebræ may supervene in cases in which lumbar punctures have been frequently performed.

The risk of introducing infection and setting up meningitis by diagnostic puncture may be practically dismissed, and is quite different from the danger of infection from repeated tappings. Recent experiments by Weed, Wegeforth, Ayer, and Felton[108] show that after intravenous injection of micro-organisms withdrawal of the cerebro-spinal fluid induces meningitis; but lumbar puncture is so frequently performed in conditions in which micro-organisms are or may be present in the blood stream, such as pneumococcic and influenzal infections, and clear fluid is drawn off without the subsequent occurrence of meningitis that in practice there is no risk that lumbar puncture alone will, by reducing the local resistance of the meninges, lead to their infection. Lumbar puncture alone thus differs from lumbar puncture followed by the intrathecal injection of horse serum, a procedure which first sets up an aseptic polymorphonuclear meningitis and then allows micro-organisms in the blood stream to invade the meninges.

Cases in which Diagnosis Remains in Doubt.

Although it is simple enough to depend for the diagnosis of meningococcic meningitis on the examination of the cerebro-spinal fluid for meningococci, there are a number of cases in which a decision is still left in doubt. Cases certainly occur about which the purely clinical diagnosis appears unquestionable, but in which the cerebro-spinal fluid, though turbid from the presence of polymorphonuclear leucocytes, does not contain any micro-organisms; thus, among 121

cerebro-spinal fluids from cases of meningitis in the French Army, Sacquépée, Burnet, and Weissenbach [97] found 6 with the features of Widal's puriform aseptic meningitis, in which no micro-organisms could be found by direct examination or by cultivation ; and Adshead,[2] in an analysis of 71 cases of cerebro-spinal fever, includes 4 with purulent aseptic cerebro-spinal fluid.

No significance, of course, can be attached to cases with a clear fluid at the first tapping and a sterile turbid fluid after a subsequent intrathecal injection of serum. The occurrence of cases with a sterile polymorphonuclear fluid at the first lumbar puncture recalls Hort's [48] contention that the meningococcus is only one of the phases in the life-cycle of the virus, and raises the unorthodox suggestion that in some of the phases the organism may be a filter-passer.

These cases should be treated, although they cannot be tabulated, as meningococcic ; recovery is in favour of a meningococcic origin, not only from the point of view of this therapeutic test, but also because other forms of polymorphonuclear meningitis are usually fatal, recoveries in pneumococcic meningitis being most exceptional.

Differential Diagnosis.

As already mentioned, the cerebro-spinal fluid, though characteristically polymorphonuclear, may, particularly in chronic cases, show a predominance of lymphocytes, and so resemble the cytology of the meningitis of tuberculosis, syphilis, mumps, malaria, acute lead poisoning, and of the meningitic form of acute poliomyelitis. Incidentally, some of the clinical differences from tuberculous meningitis have been referred to, and with regard to the others, though it is an interesting academic study, lumbar puncture will always be necessary and more rapidly and surely decide the diagnosis and prognosis.

Meningism may be due to such a large number of acute infections that it would take too long to detail them. *Pneumonia*, especially in children and in apical pneumonia in adults, may be ushered in by signs of meningeal irritation, and the absence of meningitis can only be certainly and at once settled by examination of the cerebro-spinal fluid, for, on the one hand, there may be pneumococcic meningitis, or, on the other hand, even if a patient have physical signs of pneumonia, there may also be meningococcic meningitis, as was shown by isolated cases in the Navy and by Jacobitz's [53] record of three cases of meningococcic meningitis with meningococcic pneumonia. Much the same is true of *otitis media*, which may cause meningism, or, as in five naval cases, may be followed by meningococcic meningitis.

As the onset of the two diseases may be exactly similar, both being somewhat protean in this respect, the diagnosis between cerebro-spinal fever and *influenza* with meningism can often only be made by lumbar puncture. It is especially during outbreaks, such as in the late autumn of 1918, that sporadic cases of cerebro-spinal fever are prone to be overlooked until the symptoms become unmistakable. Among a number of influenzal cases the occurrence of a case with headache more severe than usual and not yielding to treatment, stiffness of the neck, and Kernig's sign should suggest lumbar puncture.

The meningism of acute *malaria*, especially as herpes labialis is common, may suggest cerebro-spinal fever; the presence of parasites in the blood, the lymphocytosis of the cerebro-spinal fluid, and the rapid disappearance of the symptoms after injections of quinine should enable a correct diagnosis to be made. The cases of chronic meningococcic septicæmia may imitate malaria but do not react to quinine, and should be recognised by a blood culture.

After salvarsan injection meningism has in rare instances been known to occur (Sabrazes [96]). In exceptional cases prophylactic vaccination against cerebro-spinal fever has caused symptoms of meningeal irritation and simulated the onset of the disease, but the disturbance is not progressive, and even when most marked passes off in a few hours (Gates).

Tonsillitis with enlarged cervical glands by causing stiffness of the neck may, when cerebro-spinal fever is epidemic, be regarded as the more serious disease. *Rheumatic* stiffness of the neck is ameliorated by movement, whereas that of cerebro-spinal fever is aggravated and in an early stage may only be brought out by repeated movements. On account of the headache, stiffness of the neck, and the rash, *measles* and *rubella* have sometimes been thought to be meningitis. *Rheumatic fever* may be simulated by cases of cerebro-spinal fever with an acute arthritic onset, but the failure of salicylates to reduce fever and pain should render this diagnosis doubtful.

Spirochætosis ictero-hæmorrhagica may cause meningitis, and in some of these cases there may be little or no jaundice (Costa and Troisier [20]). The detection of the spirochæte in the urine and of its pathogenic effect by injection of the patient's blood and urine into guinea-pigs will establish the diagnosis.

In the *acute infective polyneuritis* described by Bradford, Bashford, and Wilson,[14] the initial symptoms of headache, vomiting, pain in the back, and moderate fever are in rare instances sufficiently severe to suggest the possibility of cerebro-spinal fever, but lumbar puncture shows that there is not any meningitis. *Anthrax* with cerebral symptoms

may imitate meningococcic meningitis. In five cases of rapidly fatal anthrax recorded by Reece [87] there were cerebral symptoms and anthrax bacilli in the cerebro-spinal fluid, but the symptoms were characteristic of cerebro-spinal fever in two only. During the same year, 1917, there were two cases of anthrax imitating cerebro-spinal fever in the Navy.[107] *Meningeal hæmorrhage* from various cause may closely imitate the early stages of meningococcic meningitis, and for a correct diagnosis examination of the cerebrospinal fluid is then essential.

The meningitic form of acute poliomyelitis.—Clinically the resemblance to cerebro-spinal fever is very close ; thus in 1911 Reece [86] found that a reputed outbreak of cerebro-spinal fever was really one of acute poliomyelitis without any admixture of meningococcic cases. Sporadic cases of meningococcic infection occurring in the summer, the favourite period of the year for poliomyelitis, and in the presence of the other disease are naturally liable to be misinterpreted ; if recovery occur a residual paralysis suggests that the disease was really acute poliomyelitis. In July, 1915, there was an outbreak of 15 cases clinically resembling cerebro-spinal fever among the youths at Shotley Barracks, but only four were proved bacteriologically to be of this nature ; consideration of the notes justified the suspicion that one might have been a case of poliomyelitis. As already mentioned, the diagnosis depends on examination of the cerebro-spinal fluid, which shows a lymphocytosis and absence of meningococci.

Encephalitis lethargica, when first seen in Paris and elsewhere, was thought to be meningococcic meningitis until lumbar puncture put this diagnosis out of court.[75] The cerebro-spinal fluid is clear and the cell content usually normal ; if there be any cytological change it is in the direction of a lymphocytosis. Another difference from meningococcic infection is the absence of a hæmic leucocytosis (Panton [83]). The striking features of the disease—lethargy and ocular paralyses, though the latter are not constant—should arouse suspicion. On the other hand, the patients may have erythematous or petechial rashes, herpes, swelling of the joints, and vomiting. When first seen some cases of meningococcic meningitis may suggest ordinary *epilepsy*, *tetanus*, or even *strychnine poisoning* ; this is especially likely to occur in sporadic cases or at the commencement of an outbreak.

Uræmia may be suggested by fulminating cases in an unconscious condition, especially as there may be albuminuria, or from collapse, suppression of urine (Robertson [93]), and a petechial rash which might be thought to be uræmic. In pregnant women convulsions during

cerebro-spinal fever have been regarded as eclamptic (Williamson [112]). In a case reported by Roberts and Ford,[91] pain and loss of power in the legs, puffiness of the face, and albuminuria were thought to be due to acute nephritis and uræmia. In fulminating cerebro-spinal fever the blood pressure is low and the extensor plantar response, obtained in uræmia, is rare.

The purpuric eruption of the fulminating and acute cases may lead to confusion with fulminating and other forms of *purpura*, such as acute lymphocytic leukæmia, streptococcic septicæmia, Henoch's purpura, and the diagnosis may be cleared up only after death (Verbizier,[106] Pape and Laroche [84]). *Hæmorrhagic small-pox* occurring in connexion with cerebro-spinal fever may be regarded as the meningococcic infection. Sir William Osler tells me that hæmorrhagic cerebro-spinal fever was recognised in Montreal in 1872, and that two years later a case of hæmorrhagic small-pox was regarded as cerebro-spinal fever until the patient's mother went sick with small-pox. In the past the disease appears to have been confused with *malignant measles*, for in 1867 Gordon [40] stated that hæmorrhagic measles always accompanied cerebro-spinal fever. The mottled rash may suggest measles, and in a case of meningococcæmia without meningitis, as in that recorded by Sainton and Maille,[100] a blood culture may be necessary to clinch the diagnosis. In *typhus* the purpuric rash does not appear before the fourth day of the disease, whereas it is an initial sign in cerebro-spinal fever. The fulminating cases may at first simulate severe *food poisoning*.

In acute *osteomyelitis of the spine* lumbar puncture may give exit to pus from the extradural space. This occurred in two cases in the Royal Navy. In neither of these were there definite symptoms of cerebro-spinal fever, but Grisel,[41] in a review of this form of osteomyelitis, states that although in some cases the symptoms of compression are quite definite and disappear when the abscess is evacuated, there are others in which the association with meningitic symptoms and septicæmia renders the diagnosis very difficult.

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LECTURE III.

Mortality and Prognosis.

Mr. President, Censors, and Fellows of the College, —In considering the prognosis it is important to have some idea of the natural history of the disease when unmodified by serum treatment. Its severity varies in different epidemics and at different periods of the same epidemic; thus it is generally believed that fulminating cases are more frequent at the beginning and mild and abortive cases towards the end of an epidemic.

From a review of 41 epidemics Hirsch in 1866 found that the mortality varied from 20 to 75 per cent., and according to Rollet the average mortality of epidemics in France up to 1844 was 51 per cent., the extremes being 28 and 75 per cent. Flexner [26] gives statistics of 18 epidemics before the serum era showing death-rates between 90 and 42·5 per cent.; of these 18 epidemics one had a death-rate of 90 per cent., two of 80 per cent., nine of 70 per cent. or more, three of more than 60 per cent., and one of 42·5 per cent. Flexner also compares the death-rates of cases in the same epidemic treated with and without serum showing a very great difference, 30, 40, or even 50 per cent., in favour of those treated with serum. Experience in the Navy also bears witness to the beneficial influence of serum:

> Among 96 cases not treated by serum 49, or 51 per cent., proved fatal and out of 105 cases treated in 1915 with serums which appeared to be inert 64, or 61 per cent., were fatal; whereas out of 295 cases treated with serum during the second, third, and fourth years of the war the mortality was 95, or 32·7 per cent.; 176 of these cases receiving Flexner's serum alone with a mortality of 51, or 29 per cent. In Belfast the mortality fell immediately from 72 to 30 per cent. on the introduction of Flexner's serum (Robb).

In quite recent years the mortality has been much higher in this country than would be expected on the assumption that serum treatment is available for all; thus Reece found that among 5306 cases in England and Wales during the years 1914 to 1917 inclusive there were 3471 or 65·4 per cent., deaths. This is more than double the percentage (30·9) of deaths among Flexner's 1294 cases treated by serum, and probably many of the British cases were untreated, or if treated with serum at all not efficiently. By intensive

treatment—namely, the intrathecal injection of 60 c.cm. within the first 24 hours, or in bad cases within 12 hours—Welsh and Brown [34] had two deaths only, or 7 per cent., among 28 cases.

Essential Factors in Serum Treatment.

The effect of serum has been shown to depend to a very considerable extent on its early use; thus Flexner found that among 199 cases in which treatment began within three days of the onset the mortality was 18 per cent.; among 346 in which treatment began after the third and before the seventh day 27 per cent., and among 666 cases in which treatment began after the seventh day 36·5 per cent. proved fatal. Netter, Dopter, Christomanos, Levy, and Flack give similar evidence. When dealing with smaller numbers of cases the mortality may not fall regularly with the delay of treatment, because the fulminating cases swell the death-rate on the earlier days, and the mild cases that are atypical and probably would recover under almost any conditions come under treatment late. In a series of 25 cases which were not given serum before the 20th day of the disease Netter [57] obtained cures in 16, or 64 per cent.

It is particularly in the septicæmic or pre-meningitic stage that early and vigorous intravenous administration of serum may cut short the disease. Herrick [41] has recently shown that the free administration of serum intravenously reduced the mortality to 18·5 per cent. from 62·5 per cent. obtained in severe cases treated either by intrathecal injection alone or by intrathecal injection combined with small amounts of serum intravenously.

Another important factor in the serum treatment is that the serum should contain the antibodies specific to the infecting strain of the meningococci. This has been insisted on widely, especially by Dopter, Netter, and Gordon. Flexner's serum from the Rockefeller Institute, which is multivalent and made by the use of 40 strains of meningococci, has on the whole given better results than any other serum; but the use of a multivalent serum, or of a pooled serum of the more probable infecting strains, until the actual type of the infecting organism is determined, when the univalent type serum is substituted, is the ideal plan.

Gordon and Hine [38] have recently published the results of the first 90 cases treated with monotypical serums made by Stanley Griffith at Cambridge in the University Field Laboratories under the direction of the Medical Research Committee. Monotypical serums have been prepared for Types I., II., III., IV., and are known as M.R.C. serum. When a case is first seen and until the type of the infecting meningococcus has been determined, injections of pooled Types I. and II. serums are given; the reasons for not giving

pooled serum of all four types are: (*a*) that if this were done, as might logically be suggested, the anti-endotoxin against the existing type would be more dilute than in the pooled serums of Types I. and II.; and (*b*) that from 80 to 85 per cent. of all cases of cerebro-spinal fever are due to infection with meningococci of Types I. or II. When the type is determined the corresponding serum is given.

Out of the 90 cases 7 were fatal solely or largely from causes other than cerebro-spinal fever, and so may be eliminated. Out of the 83 cases 34 were due to Type I. with one death, or 3 per cent.; 32 due to Type II. with 7 deaths, or 21·9 per cent.; 10 to Type III. with no death; and 7 to unknown types with 2 deaths, or 28·6 per cent. Therefore, out of the 83 cases 10 only, or 12 per cent., proved fatal.

The reason why the univalent serum for Type II. is the least successful of the monotypical serums is, as laboratory experiments show, that it contains less anti-endotoxin for the homologous meningococcus than the other serums do; this is because the Type II. meningococcus, as shown by the absorption test, is more complex than the other types. Possibly a more successful serum will be obtained by immunising horses, each against a chief sub-group of Type II. meningococcus and then pooling their serums. I have recently observed a limited outbreak of 10 cases all due to Type II., which, though vigorously treated with Type II. serum, both intravenously and intrathecally by Captain E. H. Shaw, did not react in a satisfactory manner.

Effects of Serum Treatment.

By comparison of the duration of the disease in various series of cases in the pre-serum era with 830 serum-treated cases that recovered Flexner finds that as the result of serum the period of active symptoms is shortened and the cessation of symptoms, which in the natural history of the disease is almost always by lysis, is by crisis in 30 per cent. of the cases. The effect of treatment on prognosis may also be estimated by the sequels of the disease in cases treated by the symptomatic and by specific (serum) methods. Complications appear to be less frequent since the era of serum. In the pre-serum epoch the incidence of internal ear disease varied from 12 to 33 per cent., whereas among Flexner's 1294 cases treated with serum it was 3·5 per cent.; and similarly the incidence of irido-cyclitis fell from between 4 and 10 per cent. of all cases to 1 per cent. Flexner also quotes Longo's small comparative series of cases in children showing the influence of serum in preventing hydrocephalus, deafness, or mental defects.

The factor in serum treatment that is of essential importance in bringing about a rapid and permanent cure is the early and sufficient use of a serum containing the antibodies specific to the type of infecting meningococci so as to abolish the infection, neutralise the toxæmia, and stop the meningitis before adhesions and blocking of the cerebral

ventricles are brought about. Death in the early stages may be due to septicæmia and overwhelming toxæmia, which can only be antagonised by the rapid introduction of serum intravenously; the chronic cases are generally due to loculated meningitis and closure of the foramina of the cerebral ventricles, and even with operative measures to relieve this sequel of unsuccessful early treatment by serum the outlook is very grave. Some of the chronic or subacute cases are due to meningococcic septicæmia and the prognosis is good provided the condition is recognised and serum given intravenously.

From what has been said it follows that, although the infectivity of the disease is low and a small proportion only of the population is affected, the prognosis of cases untreated by serum is bad, that the death-rate may vary in different epidemics from 20 up to 90 per cent., and is very rarely less than 50 per cent.; whereas with serum treatment the mortality should not be above 30 per cent., and, with further improvement of the methods and serum, may be much less, that the duration of attack is shortened, and the incidence of sequels diminished.

Influence of Age and Occupation on Prognosis.

Age has a distinct influence on prognosis which is bad at the two extremes of life. In infants under 12 months of age the mortality is high, mainly because the patients usually come under observation late from the difficulty in arriving at an early diagnosis, for Robb[70] and others have found that with early treatment infants do very well; the delay in cases that survive may lead to the formation of meningitic adhesions and hydrocephalus (posterior basic meningitis). Between the ages of 2 and 10 the outlook becomes very favourable, but after 40 the mortality curve rises, and in old people, in whom the disease is very rare, it may reach 100 per cent. One of the factors militating against recovery in patients over 40 is the existence of arterio-sclerotic renal disease.

Occupation.—In Australia Fairley and Stewart[23] found that the mortality was higher in soldiers than among civilians, and ascribed this to fatigue due to unaccustomed drills. In this country, however, this was not the case, as is shown by the following figures given in the first lecture:—

Years.	Deaths. Civilian population.	Military.
1914	68·7 per cent.	... 60 per cent. (from Sept. 19th only).
1915	64·9 ,,	... 49 ,,
1916	65·6 ,,	... 44·5 ,,
1917	65·4 ,,	... 44·3 ,,

Individual Symptoms in Regard to Prognosis.

The prognostic significance of individual symptoms may be considered first as regards those due to the general systemic invasion. A very acute onset with sudden loss of consciousness—the *apoplectiform onset*—has a serious outlook, as death may rapidly follow, but if the acute stage does not prove fatal recovery may eventually occur.

Among 247 cases of cerebro-spinal fever in the Navy during the second and third years of the war this apoplectic onset occurred in 12, or 5 per cent., and 6 proved fatal.

As the *fulminating* cases with large purpuric areas and a high mortality may also show cyanosis and dyspnœa, these signs are very grave prognostics; sweating is often associating with the cyanosis and dyspnœa, but alone has not the same sinister significance. The presence of a *rash* without further qualification does not affect the prognosis to any considerable degree, but a distinction must be made in this respect between the hæmorrhagic rashes, and more especially large purpuric extravasations on the one hand and the non-hæmorrhagic rashes on the other.

Among 502 naval cases 296 had rashes of some kind or another, with a mortality of 129, or 43·5 per cent., whereas of the remaining 206 cases without recorded rashes 80, or 39 per cent., proved fatal. But out of 153 cases with hæmorrhagic rashes 65, or 42·5 per cent., proved fatal, whereas out of 42 non-hæmorrhagic eruptions the mortality was 12, or 28·6 per cent. The 153 cases with hæmorrhagic rashes include both the large purpuric rashes and the petechial, and of these the former have, of course, much the graver prognostic importance.

Although it has been stated that, as in pneumonia, a low *leucocyte count* is a bad sign,[56] it is generally agreed that no prognosis as to a fatal result can be made from the leucocyte count. Similarly the *temperature* and the degree of *headache* have little, if any, ultimate prognostic significance.

As herpes labialis usually appears on the fourth day of the disease it is hardly ever seen in the fulminating cases that prove fatal within 48 hours of the onset. The good prognosis formerly ascribed to *herpes*, and to a *serum rash*, probably depends on the occurrence of death in a considerable number of the severe cases before the time for appearance of the rashes is due. Thus, out of 86 fatal cases in the Navy during the third and fourth years of the war 27, or almost a third, occurred before the fourth day of the disease. Cases with a serum rash usually do well, and Ker [46] considers that sharp attacks of serum disease exert a favourable action on the course of the disease, possibly as a result of metabolic stimulation; this view is confirmed by

Longcope and Rackemann's[49] demonstration that after serum disease antibodies to horse serum begin to appear in the blood, at first slowly and later rapidly.

Synovitis is a metastatic complication which, according to Netter, is seen in cases which eventually are cured. Possibly the local focus acts as a "fixation abscess" and raises the resistance to infection in the same manner as a vaccine. Among 24 cases of synovitis in the Navy the mortality was 6, or 25 per cent., considerably lower than the mortality for the 502 cases. *Pericarditis* is often latent, and though looked for during life may be found only at the necropsy: this occurred in the 1904–05 epidemic in New York, and accordingly Koplik[47] speaks of pericarditis as a fatal sign, but this view is unduly pessimistic. Among the naval cases it was found after death in three instances, and pericardial friction was heard in three cases that recovered.

The bearing of the *arterial blood pressure* on prognosis has been dealt with by Fairley and Stewart, who find that a low blood pressure during the first three days is associated with a severe infection, and is therefore of bad omen. The degree of the rise of blood pressure consequent on the onset of meningitis and increased intracranial pressure is important; among 116 cases with an average blood pressure above 120 mm. Hg after the third day of the disease 70 per cent. proved fatal, whereas among 120 cases with an average blood pressure below 120 mm. Hg the mortality was 21 per cent. Cerebral hæmorrhage may occur as a result of the raised blood pressure.

The occurrence of *ptosis* or *hemiplegia* points to a definite lesion and renders the prognosis grave.

As pointed out above, the mortality among 18 naval cases with ptosis was 13, or 72 per cent.; whereas that of 59 cases with strabismus (probably mainly spasmodic and not paralytic) was 31, or 52·5 per cent. Among 12 naval cases with hemiplegia 10 proved fatal.

On the other hand, *facial paralysis* or *paresis* is an early and transient event and does not cloud the outlook.

From routine examination of 184 patients, 116 of whom had optic neuritis, Fairley and Stewart found that the presence or absence of *optic neuritis* is of no value in prognosis, for out of the 116 cases 74, or 65 per cent., recovered, and the intensity of the changes did not bear any relation to the severity of the disease. *Nystagmus* occurs in grave cases and is regarded by Fairley and Stewart as pathognomonic of internal hydrocephalus. The nature of the *cerebro-spinal fluid* does not form a guide to the outcome of the case, except in so far as a large number of extracellular meningococci make the outlook bad. A purulent fluid may rapidly clear after intrathecal injection of efficient serum or a clear fluid may rapidly become purulent.

The occurrence of *broncho-pneumonia* naturally renders the

outlook very serious. Cheyne-Stokes breathing and Biot's cerebral type of *respiration*, characterised by periods of apnœa at irregular intervals, point to approaching death, as does slowing of the respiration pulse ratio from the normal 1 : 4 to 1 : 2. The respiration may fail entirely while the pulse is well maintained. According to Fairley and Stewart there is no definite relation between the respiratory rate and the intrathecal pressure as estimated by Quincke's manometer.

Finally, the prognosis is fallacious and difficult, as sudden exacerbations from reinfection may occur most unexpectedly.

Remote Prognosis.

Cerebro-spinal fever is a killing rather than a crippling disease. In the past it had a bad reputation for the number of disabilities—mental, nervous, and auditory, which in young children accounted for much deaf-mutism—left behind. But at the present time there is a general agreement that if the patient survive he is not likely, apart, perhaps, from deafness, to be permanently crippled. As already mentioned, Flexner's figures show that the incidence of complications and sequels is much diminished by serum treatment. But it is not certain that the general rarity of severe after-results is entirely due to the introduction of serum treatment; for even now a number of cases do not receive efficient serum treatment, and in 1915 the serum available in this country appeared to be inert, and yet there was no noticeable crop of disabilities. Foster and Gaskell,[33] who relied mainly on lumbar puncture in that year, noted very few sequels in their cases, and explained the greater frequency of disabilities in the past, when lumbar puncture was not in vogue, to the effects of continued increased intracranial pressure.

Mental changes do not appear to be much more frequent than after other severe diseases. During convalescence there may be some mental debility and occasionally impaired memory, but no permanent mental defect is left behind. Worster-Drought,[86] from analysis of 120 cases in 1915–17 that recovered, found that in none was there permanent mental defect. In rare instances epilepsy has followed cerebro-spinal fever; Netter [53] has seen five examples of this, but among his 253 cases that recovered this sequel occurred once only. Sainton [76] reported two cases; in one the epilepsy began a month after the disease, in the other after an interval of six months; he ascribes it to the persistence of some meningeal irritation, and Netter points out that this may be anticipated in cases with hemiplegia or partial convulsions during the acute disease.

Paralyses of various forms, apart from the ocular manifestations during the acute stage of the disease, are rare and are very seldom permanent. It is highly probable, as

pointed out by Netter and Debré,[61] that many of the permanent paralyses formerly ascribed to cerebro-spinal fever were due to acute polioencephalitis, the meningitic form of which may so closely imitate meningococcic meningitis. According to Sophian, most of the paralyses in cerebro-spinal fever are cerebral in origin, and this raises the question of the diagnosis from acute polioencephalitis in those instances in which the diagnosis of meningococcic infection has not been proved bacteriologically.

Day of Death.

More than half the fatal cases occur during the first week of the disease.

Out of 86 deaths among 225 naval cases during the third and fourth years of the war 17 occurred within the first two days or were fulminating cases, eight on the third, and 12 on the fourth day, so that 37, or 42 per cent., of the deaths occurred within the first four days. Three deaths occurred on the fifth, 5 on the sixth, and 2 on the seventh day, so that 47, or more than half the cases, were fatal within the first week. During the second week there were 15 deaths, during the third week 12, during the fourth and fifth weeks 3 each, 2 in the sixth week, 1 in the seventh week, and isolated cases on the 57th, 67th, and 90th days of the disease.

Prophylaxis.

Hygienic Measures.

Good general hygienic conditions are, of course, important in maintaining the resistance of the body to infection and so preventing the occurrence of other diseases favouring meningococcic invasion. Hence, fresh air, efficient ventilation, proper clothing, good food, the avoidance of over-fatigue, and protection from depressing conditions are desirable, particularly in the case of recruits, new entries into the Navy, and newcomers to institutions. During epidemics it is desirable, as far as possible, to temper the wind to the raw recruits and to delay vaccination and antityphoid inoculation until they have become accustomed to their new life. After vaccination and inoculation special care should be taken to avoid fatigue from drills and route marches.

As catarrhal diseases, such as influenza, catarrh, tonsillitis, and sore throat, appear to play some part in favouring the outbreak of cerebro-spinal fever, and often precede its appearance and may coincide with its prevalence, every effort to limit their spread should be made. Special care

should be taken to prevent the common use of handkerchiefs and towels. Isolation when possible should be carried out, and the cubic space in the rooms may be increased. The throats and noses, both of the unaffected and of the patients, should be sprayed with dichloramine-T or douched with a mild antiseptic lotion, such as warm solution of permanganate of potassium, 1 in 1000. When convalescent the men should be carefully protected from fatigue.

The avoidance of overcrowding is an essential factor in maintaining the general health and, further, in preventing a rise in the rate of meningococcic carriers and the consequent occurrence of cases of the disease. The importance of a sufficient cubic space (600 cubic feet) per individual and of 3 or at the least, as an emergency measure, 2½ feet between the beds when more than one person occupies a room, has been shown by Glover. It was also brought out by events at the naval barracks in the last quarter of 1918; as a result of the severe influenza epidemic in September and October an Admiralty order came out in October to the effect that the hammocks in the naval barracks should be 2½ feet distant at their nearest points and that the men should lie alternately head and feet; during October there were in the Navy 21 cases of cerebro-spinal fever, all but one in barracks or similar establishments, in November there were 6 cases (one in a ship), and in December 2.

Search for Carriers.

As the disease is spread by human carriers it should be exterminated if all the carriers were detected and isolated until they became permanently negative. At present the general public is not educated up to this ideal, and even if it were, the labour entailed by its effective performance would be almost, if not entirely, prohibitive. Further, the frequency of intermittent carriers[3] and the failure of bacteriological tests would prevent such a drastic measure from being infallible.

The question of wholesale examination of naval and military forces for carriers has been much debated, and it is clear that unless the naval and military units when thus cleared from carriers are entirely isolated from the civil population, infection will be continually re-introduced. By the order of Sir Arthur May, Director-General of the Medical Department of the Admiralty, swabs from the throats of new entries into the Navy, and drafts, were examined bacteriologically from the early part of 1916 to the end of December, 1918. Although the number of cases in sea-going ships has fortunately been low—48, or 13 per cent., out of the 360 cases—from the beginning of 1916 to December 31st, 1918, it was higher than in the first seventeen months of the war, during which the routine search for carriers was not carried

out and 17 cases, or 8·7 per cent., out of 195 cases in the Navy occurred in sea-going ships.

It therefore appears that the relative freedom of the sea-going ships from the disease depends on factors other than the search for carriers, and among them is probably the more matured condition of the crews, for the disease occurs mainly in new entries in barracks. Flexner,[26] however, from comparison of statistics from camps in which the search for carriers had been carried out with those in which this course was not adopted, considers that the incidence of the disease was lower in the former; and among the New Zealand troops isolation and disinfection of carriers before embarkation for Europe was followed by good results (Parkes).[67] On the other hand, Galambos[34] insists that the segregation and disinfection of healthy carriers are useless, as the incidence of the disease is not influenced thereby, and he quotes other German writers, G. B. Gruber, Klinger, and Fourmann, to the same effect. Gruber considers that meningococcic carriers are on a par as regards their significance with pneumococcic carriers; but this would appear to be on the assumption that isolation of pneumococcic carriers is unthinkable, whereas recent observations on carriers of virulent pneumococci show their importance. Mink[55] from his experience at the Great Lakes Naval Training Station considered the isolation of carriers quite worthless in the prevention of the disease.

Two suggested methods, short of complete search for and segregation and disinfection of all carriers in naval and military forces, may be quoted: (1) that search for carriers should only be made when a case of the disease arises, and only among the contacts, the carriers thus detected being segregated and disinfected; (2) that new entries should be examined and the detected carriers treated in a selective manner. Thus, just as in pneumococcic carriers, so also in the case of meningococcic carriers the saprophytic germs may be of the same or of a different strain from that causing the vast majority of the cases of the disease. Thus 70 to 85 per cent. of all the epidemic cases of cerebro-spinal fever are due to two strains of meningococci; and for the exigencies of the Service it has been suggested that all carriers should be treated with sprays, but that only those with large numbers of meningococci and meningococci of the epidemic strains should be isolated. These dangerous carriers would be kept isolated until four successive weekly swabs from the naso-pharynx have been shown to be free from meningococci.

Treatment of Carriers.

Fresh air and sunshine are important; the positive carriers should be kept separate from those who have become negative so as to obviate re-infection, and carriers should be

isolated according to their types so as to prevent cross infection.

In local treatment of the naso-pharynx by gargles, douches, swabbing, hand-sprays, and inhaling chambers, it is important that mild antiseptics, such as dilute solutions of chloramine-T, dichloramine-T, acriflavine, carbolic acid, carbolised solution of iodine, boracic, permanganate of potassium, sulphate of zinc, formalin, should be employed, otherwise the naso-pharyngeal mucous membrane may be so damaged that the carrier state is prolonged instead of being shortened. Gordon and Hine have supervised the construction of spraying chambers fitted up with Hine's special steam jet. The carriers should be three feet apart in the chamber and turned back to back, and in order to avoid cross infections carriers of the same type should be treated at the same time. The men may with advantage sit down, so as to obviate fainting, and should be told to breathe in through the nose and out through the mouth.

By the local application of dried antimeningococcic serum to the naso-pharynx, by means of a special apparatus provided by the Pasteur Institute, Cayrel[9] cured 23 out of 30 meningococcic carriers in three to five days. A powder composed of dried antimeningococcic serum, arsenobenzol, benzoin, and bismuth carbonate has also been employed in France, the powder being blown into the nostrils four times daily (Derriey).[21] Vaccines have been occasionally used (Chalmers and O'Farrell[11]), but their failure is not unnatural, as the carriers are probably vaccinating themselves as shown by the presence of antibodies in their blood (Gates[35]).

As transient carriers rapidly become negative spontaneously, whereas the cure of chronic carriers is prolonged and difficult, there is some difference of opinion as to the value of antiseptic sprays and other methods in the treatment of carriers.

Among 360 carriers at Portsmouth Fildes and Baker[25] found that 212 were mild carriers with an average duration of 0·45 month, 126 being positive for one week only, and 148 chronic carriers with an average duration of 2·6 months. The chronic carriers were nearly all of the less pathogenic Types II. and IV., the latter being twice as numerous as the former. They also conclude that 33 per cent. of their carriers recovered spontaneously and that about 50 per cent. of those treated by various antiseptic sprays recovered, and that none of the methods had any conspicuous merit, the difference between 50 and 33 per cent. being due not to the efficacy of treatment but to the fact that the figures were calculated from two series of men.

At another naval depôt nine chronic carriers were rapidly cured by chloramine-T in an inhaling chamber. But at camp McClellan Robey[71] found that some carriers cleared up rapidly and that others were unaffected by various sprays four times daily, and concludes that sunshine and warm fresh air were more effective than spraying in clearing the naso-pharynx of meningococci.

Cleminson's [13] work suggests that the resistance of chronic carriers to disinfection may be due to factors in the carriers rather than to inefficacy of the sterilising methods. The accessory sinuses appear to be the chief sites of the saprophytic meningococci, and "firm mucous contact" between the middle turbinals and septum on the one hand, and the outer wall of the nose on the other, obstructs the ostia of the sinuses and so prevents the access of the antiseptic spray to the infected sinuses. To shrink up the mucosa, to dilate the ostia of the sinuses, and so allow free access of the antiseptic, a spray of adrenalin chloride 1 in 6000 saline solution was used before the flavine or other spray, and was followed by improvement in the results. It is also suggested that partial turbinectomy by throwing open the ostia of most of the accessory sinuses might accelerate the cure of chronic carriers; but the results of this procedure, if it has been extensively carried out, are not known. Cleminson finds that other factors rendering chronic carriers resistant to treatment are pyorrhœa alveolaris and pre-existing infection of the sinuses.

Precautions against droplet infection should, of course, be observed by those in attendance on cases of the disease; masks should be worn and the naso-pharynx frequently washed out with a mild antiseptic solution. The throats of nurses and attendants should be periodically swabbed for bacteriological examination.

Preventive Vaccination.

Prophylactic vaccination of the general population by meningococcic vaccine has been carried out when an epidemic outbreak is anticipated. A multivalent menigococcic vaccine was found by Sophian [80] and Black [5] to afford a high degree of protection lasting for 12 months, and after the outbreak of war this prophylactic measure was more extensively tested in England (Greenwood [39]), America (Gates), and in the Sudan (Chalmers and O'Farrell).

Greenwood reports that of 4000 persons inoculated twice at a week's interval, none had the disease, and with the caution of an expert statistician concludes that a prima facie case in favour of prophylactic inoculation has been made out. Among 3700 volunteers inoculated Gates found that three men who had received two or three injections had cerebro-spinal fever; in two of these the injections were probably given during the incubation period of the disease, but the third patient should have been immune when he went sick. Gates demonstrated specific meningococcic immune bodies in the blood serum of the inoculated men as compared with normal controls.

The dosage has varied in the hands of different clinicians: Chalmers and O'Farrell began tentatively with 5 million

meningococci and did not get above 100 million ; in Greenwood's cases a first injection of 250 to 300 millions was followed a week later by 1000 millions ; Sophian and Black gave injections at weekly intervals of 100, 500, and 1000 millions, and Gates employed three injections, also at weekly intervals, of 2000, 4000, and 4000 or 8000 and found that these rarely caused more than the mildest local and general reactions. In exceptional cases with unusual susceptibility to the vaccine severe symptoms of meningism, sometimes suggesting the onset of meningitis, followed ; but these manifestations did not last more than a few hours. According to Whitmore, Fennel, and Petersen [85] a multivalent meningococcic lipovaccine—namely, with an oily suspension, as in the T.A.B. lipo-vaccine of Le Moignic—diminishes the risk of a local reaction.

Serum Treatment.

Serum treatment, which, though first employed by Jochmann, is chiefly due to Flexner's exertions, has greatly diminished the severity and mortality of the disease. As this was discussed in the section on prognosis no further figures need be brought forward ; but the serum treatment must be efficient, and it is probably due to failures in this respect that the civil mortality (65 per cent.) in this country, as shown by Reece's figures for 1914–17, is so much higher than statistics published from hospitals.

Importance of Specificity of the Serum.

The use of serum is not so simple or so uniformly successful as that of antidiphtheritic serum, which is antitoxic, whereas antimeningococcic serum, possessing bacteriolytic, bacteriotropic (opsonic), and anti-endotoxic properties, is more likely to fail in its powers as a whole. Gordon [37] found that the anti-endotoxin in deficient in a considerable proportion of the samples of antimeningococcic serum supplied for therapeutic use, although they contained a good supply of opsonin, and that the clinical potency of a serum depends on its anti-endotoxic capacity. The existence of different types of meningococci with specific antibodies renders the success of the serum treatment less certain than in the case of antidiphtheritic serum. The widespread failure of the antimeningococcic serums available in 1915 in this country appeared to depend on the absence of antibodies specific to the infecting organisms, and stood out in striking contrast to the results obtained in 1916, when Flexner's multivalent and other serums were available.

The establishment of different types of meningococci and as a corollary the preparation of homologous serums so that

a multivalent or pooled serum is given until the type of the infecting organism is determined when the specific univalent type serum is substituted, has already, as shown by Gordon and Hine's analysis, greatly improved the results of serum treatment. The extreme importance of specificity in the serum treatment of the disease and the absence of any benefit from non-specific treatment, or protein shock therapy, of which an extensive trial has unintentionally been made, are noteworthy.

The important question, indeed, may be raised whether the intrathecal injection of inert serum may not do positive harm. As already mentioned, horse serum sets up an aseptic meningitis and favours the passage of meningococci through the meninges. It might, on the other hand, be argued that the increased number of phagocytes thus provided might do good. But it is significant that in 1915 the mortality among the naval cases treated with serum intrathecally was higher (61 per cent.) than among those treated in other ways (41 per cent.); and in this connexion another series of naval cases in that year may be quoted: among 21 cases treated with soamin alone there were seven deaths, or 33 per cent., whereas among 18 cases that received both soamin and antimeningococcic serum intrathecally there was a mortality of 11, or 61 per cent.

Some Difficulties in Serum Treatment.

The nature of cerebro-spinal fever differs from that of diphtheria, and may be regarded in the first place as a general hæmic infection or invasion which later, but not necessarily, attacks the meninges, whereas diphtheria is, like tetanus, a local infection which produces a toxæmia. As a result of the meningococcæmia, foci of infection, unaffected by intrathecal injection of serum, may persist and cause recrudescences of meningitis. Further, inflammation of the meninges, like that of other serous membranes, is prone to set up adhesions and so produce isolated loculi where the infective process, being out of the reach of the intrathecal injections of serum, continues to cause symptoms. Another result is that the foramina of exit of the cerebral ventricles become obstructed and the ventricles become distended with turbid fluid containing meningococci, or eventually a sterile hydrocephalus results. The persistence of symptoms from a general meningococcæmia or from an encysted infection, especially of the cerebral ventricles, may lead to a prolonged course of intrathecal injections which may cause grave symptoms and from the nature of the case cannot do good; for in these circumstances an intravenous or intra-ventricular injection of serum is required.

As another explanation of the failure of serum treatment it has been suggested that the meningococci may become fast

to the serum, but this hypothesis must not be allowed to minimise the importance of giving a serum strictly homologous to the type of the infecting meningococcus.

Another factor rendering the serum treatment difficult is the occurrence of phenomena, variously called sero-toxic meningism or acquired intolerance of the meninges, about the time that the ordinary manifestations of serum disease are due. The symptoms resemble a relapse, but the cerebro-spinal fluid does not show meningococci and does contain sugar. If in these circumstances a fresh injection of serum be given, the patient may manifest severe pain, become delirious, show definite signs of meningitis (*vide infra*), and often goes down hill.

Human Serum.

In addition to the serum of immunised horses, the serum from convalescent patients has often been tried. In 1907 Ivy Mackenzie and Martin [51] treated 16 acute and 4 chronic cases with serum from convalescent patients, the average amount injected intrathecally being 15–20 c.cm., and obtained 10 recoveries among the acute cases (2 receiving their own blood serum). Fairley and Stewart recently modified this procedure by adding 5 c.cm. of blood serum from convalescent patients, proved to have a negative Wassermann reaction, to 20 c.cm. of a potent antimeningococcic serum. The addition of human serum was made with the object of reinforcement of complement. The mortality of the 10 acute cases thus treated was 30 per cent., whereas that of acute cases treated by serum without complement reinforcement was 50 per cent. It is obvious that when blood serum from a convalescent patient is employed for treatment, the type of the infecting meningococcus should be the same in the donor as in the recipient.

SERUM TREATMENT IN VARIOUS FORMS OF THE DISEASE.

The serum treatment of cerebro-spinal fever may be divided into : (I.) That of the general systemic infection before the meninges have been infected, or of the pre-meningitic stage ; this is effected by the intravenous injection of antimeningococcic serum. The hypodermic or intramuscular injection of serum has also been advocated, but appears to be less effective for this purpose. (II.) That of meningococcic meningitis by the intrathecal injections of serum. (III.) That of closed meningococcic infections of the central nervous system, for example, of the cerebral ventricles or of foci isolated by adhesions from the intrathecal space, and so out of reach of serum introduced intrathecally after ordinary lumbar puncture. (IV.) That of other foci of meningococcic

infection, the joints and the eye, by the local injection of serum. This category is insignificant in importance to the others.

(I.) *Serum Treatment of the Pre-meningitic Stage by Intravenous Injection.*

Comparatively recently it has been more generally realised that in the earliest stage of cerebro-spinal fever there is a blood invasion or septicæmia, and that this is usually, but not invariably followed by meningeal infection, and as a corollary that in this pre-meningitic stage the proper course is to introduce the antimeningococcic serum into the blood stream.

In addition it appears that the intrathecal injection of serum before the meningococci have invaded the meninges is not a harmless procedure. Austrian[1] proved experimentally that meningococci injected into the blood stream do not pass through the meninges and set up meningitis; this is prevented by the barrier set up by the meningeal-choroidal complex, and recalls Sherrington's[79] observation that healthy secreting membranes are not pervious to the bacteria. But Flexner and Amoss,[29] as well as Austrian, have shown that the defence of the meningeal-choroidal complex is broken down by injury, as can be done by the intrathecal injection of horse serum with resulting aseptic meningitis. The premature intrathecal injection of serum—namely, before the meninges have allowed meningococci to pass through, may thus determine meningitis.

The most efficacious method of introducing the serum into the blood stream is obviously by intravenous injection, and from experience of more than 100 patients thus treated Herrick[42] finds that it is both satisfactory and safe. His treatment aims at the sterilisation of the blood before the meninges have become affected and is an advance on the usual methods which are concentrated upon the later stage when meningitis is established. Large quantities (200–600 c.cm. in all) of serum are given intravenously and, when there is meningitis present, active spinal drainage and comparatively small intrathecal injections of serum are carried out. No bad effects followed the large intravenous injections and serious anaphylaxis was seen in only one case. Goldon[36] found that intravenous injections of 20 to 40 c.cm. were usually followed by more or less shock, with failure of the pulse and respiration, lasting about 15 minutes, and followed by a rigor and a rise of 2° to 4° of temperature.

Of the four classes of cases—the abortive, the ordinary, the severe, and the fulminating—Herrick's most brilliant results were obtained in the severe cases, the patients often coming out of coma with rapid recession of the rash and

symptoms so that in 48 hours many are apparently out of danger; large intravenous injections reduced the mortality of the severe cases from 64 to 19 per cent. Subacute and chronic cases with cachexia, delirium, and other distressing symptoms are seldom seen, the course of the disease is shortened and the incidence of complications diminished. Out of Herrick's 265 cases 64, or 25 per cent., proved fatal, but out of 137 given ordinary intrathecal injections and less than 45 c.cm. intravenously 47, or 34 per cent., proved fatal, whereas out of 128 treated intrathecally with small doses and intravenously with large doses (50 to 800 c.cm. in all) of serum 19, or 15 per cent., proved fatal. In mild cases good results followed either of these forms of treatment. Goldon usually found that one intravenous injection was sufficient, and then, if meningitis was present, gave intensive intrathecal injections; out of 138 cases 29, or 21 per cent., proved fatal, but 16 of these were admitted in an unconscious state with a purpuric rash.

Some French physicians, such as Netter,[59] Sainton,[77] and Brulé,[8] while fully recognising the principle that in the pre-meningitic stage serum should be introduced into the circulation and that brilliant results may thus be obtained, consider that intravenous injection is too dangerous, and that in most cases it is wiser to employ hypodermic or intramuscular injections. In adopting this conservative attitude they are, of course, fully aware of Besredka's method of desensitisation.

(II.) *Serum Treatment of Meningococcic Meningitis.*

The treatment of meningococcic meningitis by intrathecal injections of antimeningococcic serum, which exerts a bacteriological action on the meningococci, favours their phagocytosis, and contains an anti-endotoxin, was introduced by Flexner and Jobling[32] in 1907 on the grounds that the antiserum is thus brought into direct contact with the focus of infection and inflammation, and that the passage of colloids from the blood stream into the cerebro-spinal fluid is a slow and imperfect process in health, and probably also in inflamed states of the membranes. In 1917 Flexner[27] restated the position and pointed out that, as very little serum from the blood reaches the inflamed meninges, it is useless to inject it subcutaneously or intravenously in the expectation that it will exert any influence on meningococci in the subarachnoid space. In the same year, however, in conjunction with Amoss,[30] he showed that in acute poliomyelitis the immune bodies, though they do not pass through healthy choroid plexus from the blood to the cerebro-spinal fluid, are able to traverse them when inflamed; if this hold good as regards meningococcic meningitis, his earlier argument is partially weakened; but this is only of academic

interest, for the success of intrathecal injection of serum in meningococcic meningitis has been proved beyond all question, and this method has superseded the easier one of hypodermic or intramuscular injection.

Doubtful cases should be submitted to lumbar puncture at once ; if the fluid be turbid serum should be given ; but if it be quite clear serum should be withheld unless meningococci be subsequently found, as the aseptic meningitis set up by serum may facilitate the passage of meningococci from the blood into the subarachnoid space. If the cerebro-spinal fluid be sterile, and especially when a blood culture shows meningococci, intravenous injections of serum should be given without delay ; and, as the septicæmic stage of cerebro-spinal fever lasts on into the meningitic stage, the intravenous injections should be continued for a time, together with intrathecal injections.

Lumbar puncture and the injection of serum should be performed under a general anæsthetic or under the influence of an injection of scopolamine 1/100 gr., morphine 1/6 gr., and atropine 1/100 gr. in 5 minims of water, as employed at Haslar by Surgeon Lieutenant-Commander Adshead. The serum should be run in slowly and in a quantity smaller than that of the cerebro-spinal fluid removed ; 20 to 30 c.cm. of serum should be given twice daily for some three or four days, for by this intensive treatment the best results are obtained. The continuance or omission of the injections is decided on the state of the cerebro-spinal fluid, the patient's general condition, and the temperature. With the new Medical Research Committee's serum the pooled serum corresponding to type I. and II. is given until the type of the infecting meningococcus is established, and then the corresponding monotype serum is substituted. The access of serum to the base of the brain is facilitated by raising the foot of the bed, and Ramond [69] recommends that the patient should lie for a time on his face in order to direct the serum to the region of the optic chiasma.

When any recrudescence or relapse appears serum treatment must be at once started again ; when an interval of 10 days or more from the last injection of serum has elapsed steps must be taken to desensitise the patient, otherwise severe anaphylactic symptoms may appear ; a very small (0·5–1 c.cm.) hypodermic injection of serum may be given 4 hours before the curative dose of serum is given intrathecally, or Besredka's method of rapidly repeated intravenous injections of minute but progressively increasing amounts of serum may be employed, which though elaborate obviates the delay necessitated by the simpler hypodermic method. Before the curative dose is given, 1/75 gr. of atropine should be injected hypodermically. As mentioned elsewhere, an anæsthetic prevents the occurrence of anaphylactic symptoms.

In order to prevent the accumulation of pus and fibrin in the subarachnoid space and the subsequent formation of

adhesions, *irrigation with saline solution* is often practised, and an isotonic solution of sodium citrate (3·8 per cent.) has been recommended for this purpose by Rosenthal.[74] J. J. O'Malley[65] contrasts the results of simple lumbar puncture and administration of serum among 36 patients with a mortality of 33 per cent. with those of the same procedure with the addition of saline irrigation among 15 cases with a mortality of 13 per cent. Sheffield Neave has washed out the intrathecal space with saline solution containing 0·5 per cent. carbolic acid with beneficial results. In this connexion attention should be drawn to Flexner and Amoss's[31] results showing that lysol and protargol fail to benefit experimental meningococcic meningitis and exert an adverse influence by diminishing leucocytic emigration and phagocytosis.

The *number of intrathecal injections* of serum should be carefully considered, for it is probable that harm may result from a large number of lumbar punctures. Thus the cerebro-spinal fluid continues to collect, and as a result of repeated withdrawals an excessive secretion of cerebro-spinal fluid, perhaps comparable to cerebro-spinal rhinorrhœa, may be induced. Some prolonged cases, probably those with adhesions, appear to become resistant to serum, and sometimes intrathecal injections are followed by aggravation of the symptoms, such as headache and opisthotonos. Herrick who considers that signs of chronic or subacute caudal myelitis are common in convalescents as a result of injury from the needle, or the injury of serum, advises that if a satisfactory response does not occur after eight or ten intrathecal injections the injection should be discontinued and simple lumbar puncture performed only when signs of increased pressure demand it.

Grave symptoms and even sudden death during intrathecal injections have been ascribed to various factors, such as anaphylaxis, liberation of toxins by rapid lysis of meningococci, the toxic action of phenol often employed to preserve the serum, and, most important of all, increased intracranial pressure and distension of the closed cerebral ventricles. To avoid this a smaller quantity of serum than that of the cerebro-spinal fluid removed is important, and the gravity method of administering intrathecal injections has been advocated and practised, especially in America.

The blood pressure was found by Sophian to be lowered by lumbar puncture, and still further depressed by intrathecal injection of serum; he therefore employed blood-pressure observations as a guide to the amount of serum injected. Fairley and Stewart, however, found that the effect of lumbar puncture on blood pressure was variable, a rise being almost as common as a fall, and an initial higher pressure being followed by a fall and vice versa; but they agreed with Sophian in finding that a fall of blood pressure was commoner than a rise after intrathecal injection of serum.

MacLagan [52] has never seen a dangerous fall of blood pressure from the gradual intrathecal injection of serum, and few authors appear to have thought it necessary to control the administration of serum by blood-pressure estimations.

Roskam [75] argues that an important factor in causing collapse, respiratory failure, and coma, after the intrathecal injection of antimeningococcic serum in quantities larger than that of the cerebro-spinal fluid removed is the presence of adhesions or lymph blocking the passage of fluid from the subarachnoid spaces into the ventricles. If these apertures be blocked, increased intracranial pressure is brought to bear on the brain and medulla. On the other hand, when the apertures remain patent the fluid passes into the ventricles and there is no increased pressure exerted. Whenever acute symptoms occur after intrathecal injection of serum the fluid should be allowed to run out of the theca, and hypodermic injection of atropine should be given, and if necessary, artificial respiration carried out.

Intrathecal injections of serum in rare instances are followed by *secondary infections* through the puncture wound, especially after a large number of lumbar punctures, with a rapidly fatal issue. I have notes of several cases of secondary streptococcic infection thus produced. Secondary infection may also occur through the blood-stream, and, as mentioned in Lecture II., Netter and Salanier [63] considered that this may be favoured by the injection of large quantities of serum, especially if it be not the type serum.

(III.) *Treatment of Closed Meningococcic Infections.*

Next to be considered is the treatment of closed meningococcic infections of the central nervous system which cannot be reached by ordinary intrathecal injections of antimeningoccic serum. In chronic cases in which lumbar puncture is either dry or brings away clear and sterile fluid, but in which the symptoms persist unaltered by intrathecal injection of serum, there may be adhesions cutting off parts of the spinal intrathecal cavity or more frequently closing the foramina of exit of the cerebral ventricles.

In some cases lumbar puncture is performed higher up so as to obtain cerebro-spinal fluid above the adhesions, and if turbid meningococci-containing fluid be obtained intrathecal injection of serum can be given. Cantas of Athens advocates superior vertebral puncture between the sixth and seventh cervical vertebræ, and this has been performed in some instances, but it is obviously dangerous from the risk of injuring the spinal cord.

When from the symptoms there is reason to believe that there is a closed infection of the cerebral ventricles—ependymitis or pyocephaly—the logical course is tapping and the injection of antimeningococcic serum. This method,

practised first by Cushing and Sladen,[13] can be comparatively easily done in the infant before the anterior fontanelle is closed. Marcland collected 11 cases with 5 cures due to ventricular tapping, and contrasts these with 7 cases of untreated ventricular distension in infants found at the necropsy. In adults trephining and subsequent injection of serum is a more formidable procedure, and, according to Marcland,[54] there were 4 cures among 18 cases; more recently Landry and Hamley[48] had 1 recovery out of 5 cases trephined and injected, and Fairley and Stewart's 9 cases of trephining and drainage all proved fatal, though in some instances life was prolonged. It appears to be a desperate remedy for a desperate condition.

Stetten and Roberts[81] advocate the production of a wide opening in the corpus callosum, thereby obtaining prolonged drainage; this method is preferable to puncture with a trocar, which gives temporary relief only and so must be repeated. They record a successful result in a soldier aged 19. If necessary serum can be injected into the ventricles. In two desperate cases (one recovery) Cazamian[10] employed the orbito-sphenoidal route, practised by Bériel for the injection of salvarsan in general paralysis of the insane. In place of trephining and drainage Herrick recommends Cobb's method of breaking down adhesions around the foramen magnum and fourth ventricle by manipulations of the head under chloroform in order to relax the rigidity of the neck muscles. This method, which might suggest dangerous traction on the roots of the vagus, was often successful in causing a flow of cerebro-spinal fluid, and in one instance brought back respiratory movements after they had stopped.

A much less serious procedure advocated by Bloch and Hébert[6] for cases in which the meningococci may be encysted in situations in contact, but not in communication, with the meninges—for example, the fibro-vascular tissue of the choroid plexus—is the intravenous injection of serum. Intramuscular injection has also been employed for this purpose, but it is less likely to be successful. In this connexion Chiray's[12] description of the "reflex sign of pyocephaly" may be mentioned; in a few cases minute intravenous injections of serum, such as are used in Besredka's method of anti-anaphylaxis, are followed immediately by transient but intense vasomotor, respiratory, and cardiac disturbances.

(IV.) *Serum Treatment of Other Foci.*

Injection of antimeningococcic serum (5 to 10 c.cm.) is commonly advocated for suppurative arthritis due to meningococcic infection, but it is seldom necessary in this country. Serum has also been introduced into the pericardium, and even into the vitreous humour of the eye (Netter[60]).

Serum Disease.

In the main the serum rash and other manifestations are much the same after intrathecal as after hypodermic or intramuscular injection; but some difference would naturally be expected on account of the injection into the close neighbourhood of the central nervous system. Serum disease in man is generally regarded as anaphylactic, but it must be borne in mind that there is a striking difference between the way in which man on the one hand and animals on the other hand react to a first injection of a foreign protein; in animals, and the problems of anaphylaxis have naturally been more elaborately studied in them than in man, the primary sensitising injection is not followed by the train of symptoms so familiar in man.

Frequency of Serum Reactions after Intrathecal Injections.

Flexner[28] remarks that possibly the manifestations of serum disease are more frequent after the intrathecal than after the subcutaneous injection of serum; and from comparison of the naval cases of cerebro-spinal fever with the reported incidence of serum disease in diphtheria I was at first inclined to this view, but further sifting of the evidence did not show that there was any proof of this, and Claude Ker,[46] who also investigated this question, came to the same conclusion.

Flexner's serum, which by the generosity of the Rockefeller Institute has been mainly used in the Navy, appears to be particularly prone to cause a rash; thus among 121 naval cases that recovered or survived more than ten days 81, or 67 per cent., had a serum rash, and among Ker's cases the percentage was even more—namely, 77. But this is not higher than the incidence (67 to 81 per cent.) of serum rashes in some series[72] of cases of diphtheria specially studied from this point of view. The variations in the incidence are therefore more probably due to peculiarities in the horses supplying the serum than to the method of injection. From comparison of series of naval cases it appeared that a serum rash was commoner in cases receiving intrathecal injections alone than in cases having both intrathecal and subcutaneous injections of serum.

Relation of Manifestations to Amount of Serum Injected.

Clinical experience shows that the severity of the rashes and other manifestations of serum disease varies directly with the amount of serum injected.

Serum disease, according to Longcope and Rackemann[49]

depends on a reaction between the injected serum, which acts as the antigen, in the blood and antibodies formed in the cells of the tissues. During the incubation period of serum disease there is a constant amount of the foreign serum in the blood but none of the antibodies; when an explosive union between the antigen and the antibodies occurs the manifestations of serum disease follow, and their intensity depends on the amounts of antigen and antibodies present. If the amount of antigen be large and that of the antibodies small the manifestations of serum disease will be severe, prolonged and relapsing, and vice versa. The antibodies only begin to be extruded into the blood after the serum disease begins, and are a protective mechanism against these manifestations.

It is therefore obvious that the smaller the bulk of serum injected the less likely is serum disease to be severe, and this appears to have been shown by the rarity (3 per cent.) of serum rashes after the prophylactic injection (2–3 c.cm.) of the concentrated antitetanic serum (O'Brien[64]). But although, *caeteris paribus*, it is desirable to have a concentrated serum so as to avoid troublesome serum reactions, it is essential that the process of concentration should not diminish its curative powers, and in this connexion it is important to note that Miss A. Homer[44] has found that the immune bodies in antimeningococcic serum are mainly associated with the pseudo-globulin, and therefore that attempts to concentrate the serum by methods involving a heat denaturation of the serum proteins would considerably diminish the antibody content of the serum.

Serum Rashes.

It was stated by Currie[17] that an injection of antidiphtheritic serum just before a serum rash due to a previous injection might be expected may determine the appearance of a rash which otherwise would not have developed. Examination of the notes of the naval cases did not show that this sequence is established in cerebro-spinal fever. It is true that in a few cases lumbar puncture and the injection of serum have been performed the day before the rash appeared, there having been a previous interval of some days without the administration of serum. But such cases are, perhaps, more satisfactorily explained by the view that the symptoms which led to the lumbar puncture and the injection of serum were premonitory of the serum rash.

The serum rash is usually urticarial, erythematous, or morbilliform, and extremely irritating, but it may be scarlatiniform. In rare instances it is hæmorrhagic; this may occur in association with a sore throat or an infected wound or boils; cases of this kind have occurred in the Navy. But all cases in which a serum rash becomes hæmorrhagic are not explained by the presence of infection. Landry and

Hamley [48] mention a hæmorrhagic serum rash which was thought to be evidence of post-meningitic septicæmia until a blood culture proved negative. In another condition—namely, true anaphylaxis, the rash may be hæmorrhagic.

On the forty-eighth day of the disease, not having had any serum for 27 days, a man had an intrathecal injection of 20 c.cm.; seven hours later he vomited, had a purpuric rash, and was gravely ill. Next day the rash had faded but the right knee was full of fluid. He died seven days after the injection.

Quite commonly a serum rash appears, fades, and about two days later again becomes prominent; the first may be erythematous and the second urticarial, and both extremely irritating. These may be regarded as phases of the same reaction. In rare instances two serum rashes appear at such an interval as to justify the term double serum rash and to suggest two separate reactions, which might be supposed to be the result of injections on different days; a number of Currie's cases bear this interpretation. This, however, is not universally true, and the occurrence of two or three distinct rashes after a single injection of serum is now thought to be due to the successive appearance, at different time intervals, of sensitiveness to the different proteins—euglobulin, pseudo-globulin, and albumin—present in horse serum (Dale and Hartley[19]).

Arthritic and Other Manifestations of Serum Disease.

Another manifestation of serum disease is arthritic pain or less often effusion into the joints. The recognised association of erythematous skin eruptions and joint symptoms is explained by the assumption that the synovial membranes show changes similar to those in the skin. The arthritic manifestations are less frequent than those of the skin, but they occasionally occur without any recognisable cutaneous rash. The arthritic symptoms may accompany, precede, or, and this appears to be more usual, occur some three days after the appearance of the rash. Pain or stiffness is commoner than effusion. It does not appear that patients who have had early effusion into the joints from meningococcic infection are more liable than others to get seric arthralgia or effusion into the joints. The arthritic manifestations are toxic, and, like those of "scarlatinal rheumatism," do not react to salicylates.

In a small number of cases the serum rash is accompanied by œdema of the eyelids, scrotum, hands, and other parts, and at the same time there may be transient albuminuria. As the serum rash is so often urticarial it is not surprising that œdema—or "serous hæmorrhage" into the skin—should sometimes occur. Here it may be mentioned that

the administration of calcium lactate gr. xv. for six doses, some days before the manifestations of serum disease are expected, may be tried in order to obviate them.

In some instances transient deafness about the time of serum disease may possibly be a manifestation of that condition (A. C. MacAllister); and I have been told by Captain E. H. Shaw, R.A.M.C., of transient loss of vision at the time of the serum disease As an exceptional event de Verbizier's [82] case of severe epileptic convulsions with the status epilepticus coinciding with a well-marked serum rash and arthralgia in an epileptic, who had not had any fits during the fever, may be mentioned.

Seric Meningism and Meningitis.

The fever and constitutional disturbance preceding or accompanying the other manifestations of serum disease may be associated with recrudescence of meningitic symptoms, and a relapse is thus naturally suggested. This rare meningeal manifestation of serum disease is peculiar to intrathecal injection of serum, and though it occurs in a small proportion of cases should be more widely recognised in this country in view of the recent increase of cerebro-spinal fever. It has not, however, passed unnoticed. Netter and Debré [62] in 1911 gave a good account of it, and regarded it as a result of serotoxic œdema of the meninges. It may also be added that, as the mucous membranes originally attacked by diphtheria are liable to swell at the time of the serum reaction, an analogous sequence may be suggested in the case of meningococcic infection of the meninges.

If the *meningism* is part of the serum disease to be expected after intrathecal injection, the question arises why it is not noted more often. It does not appear to result from large quantities of serum given, for out of the nine naval cases showing these meningitic symptoms eight had less than 100 c.cm., and four of these eight less than 50 c.cm.; nor can it be explained as due to an intrathecal injection within a very few days of the appearance of the serum rash. That it is connected with some hypersensitiveness of the meninges is probable enough, but it is impossible to go beyond this vague statement.

These symptoms can be distinguished from a true recrudescence of meningococcic meningitis, for which an injection of serum is urgently necessary, by examination of the cerebro-spinal fluid for meningococci and the presence of sugar. If the cerebro-spinal fluid is clear, contains sugar, and is free from meningococci, there is no recrudescence of infection, and fresh intrathecal injection of serum may be followed by very severe pain, delirium, and other signs of meningitis. This is what Dopter [22] calls *seric meningitis*,

and he explains the symptoms as due to the formation of a precipitate in the cerebro-spinal fluid.

Anaphylaxis.

True anaphylaxis may occur in a patient who has some time previously had an injection of serum, e.g , for diphtheria or as a prophylactic against tetanus, Although in the case of ordinary subcutaneous injections of serum anaphylaxis is, as a rule, more interesting than serious in its manifestations, the effect of an intrathecal injection of serum in a sensitised person, though fortunately uncommon, may be very grave. Although anaphylactic shock does not always occur when it might be expected, it is obviously advisable before giving the first intrathecal injection of serum to inquire if the patient has ever had a previous injection. If he is unable to give any information and there is reason to suspect that he has had an injection of serum—for example, evidence of a wound in a soldier from the front—the patient should, before receiving a curative intrathecal injection be desensitised. *(Vide supra.)*

The anaphylactic symptoms are severe collapse, fall of blood pressure, rapid and feeble pulse, pallor, vomiting, feeling of thoracic constriction, failure of respiration, rapid eruption of urticaria or even of a hæmorrhagic rash. In order to counteract these symptoms the injection of adrenin and atropine has been recommended.

In several cases in the Navy intrathecal injections of serum were given after an interval from the last injection sufficiently long for anaphylaxis to have fully developed, but lumbar puncture was performed under a general anæsthetic and symptoms of anaphylactic shock did not appear. Besredka pointed out that if the nerve cells are anæsthetised anaphylactic shock is prevented.

A man had cerebro-spinal fever in May, 1917, and recovered after having 110 c.cm. of Flexner's serum followed by a serum rash. On Feb. 19th, 1918, he again had cerebro-spinal fever; after one injection of 20 c.cm. of Flexner's serum he remained well for 23 days, when a relapse occurred; he then had two injections of Flexner's serum (20 c.cm. on each occasion) and recovered. These three injections were given under chloroform and ether and were not followed by any anaphylactic symptoms; both the attacks were bacteriologically proved to be meningococcic infection.

VACCINES.

Curative vaccines have been mainly employed in subacute or chronic cases when serum appears to be losing its effect, and in a number of cases has been followed by improvement and recovery. Most writers speak of the treatment in a non-

committal tone, and Herrick argues that as relapses occur vaccine treatment is unlikely to be effective. Among 21 naval cases given a meningococcic vaccine, always in addition to other treatment, 5, or 23·5 per cent., proved fatal, the mortality of the 509 cases in the first four years of the war being 213, or 41·8 per cent. The vaccine should be autogenous, and may with advantage be sensitised. The dose varies in the hands of different workers:

Chalmers and O'Farrell[11] gave 200 million dead meningococci for the first dose and 500 millions two days later, and out of ten apparently hopeless cases had four recoveries. Boidin[7] gave every three or four days 200, 350, 500, and 750 millions. MacLagan[53] recommends 50 to 100 millions for the first dose, which is repeated and increased every three or five days. Fairley and Stewart[23] begin with 50 millions and increase by that amount until 600 millions are given; out of 52 subacute and chronic cases 17, or 32 per cent., proved fatal, and of these 13 had internal hydrocephalus, the mortality of the remainder being only 7·7 per cent. Warren Crowe[16] and Colebrook,[14] who recommended vaccines much earlier in the disease, about the second or third day, gave much smaller doses, 1 million and 7½ to 20 millions respectively. These two workers wrote of the epidemic of 1915 when the serum available in this country was inert. The usual reaction is slight, with some headache and fever.

In serious cases Boidin recommends the production of a "fixation" abscess by the injection of 1·5 c.cm. of turpentine into the subcutaneous tissues of the thigh, in addition to the use of an autogenous vaccine, and reports that as a result there is often definite improvement and sometimes cure when the abscess is opened; in some cases he found it necessary to produce a second "fixation" abscess.

Other Methods of Treatment.

Apart from meningococcic serum, and perhaps vaccines, other forms of treatment are of very subordinate importance and, except when serum cannot be obtained or is inert, as it appeared to be in this country in 1915, are mainly of historical interest.

Surgical Measures.

Lumbar puncture temporarily relieves pressure and headache, but it is not an efficient radical measure; the drainage is at best intermittent, and from this point of view the more drastic method of laminectomy and draining the spinal subdural space is more logical. This was done in the pre-serum days; Osler[66] referred to unsuccessful cases operated

upon by Cushing (2) and one under J. H. Musser's care. In 1899 the late Herbert Allingham [73] performed laminectomy in a patient under my care who recovered with complete deafness, but the case was not bacteriologically proved to be meningococcic. In posterior basic meningitis the occipital bone has been trephined and the posterior subarachnoid cistern drained (Ballance [2]).

In a brief review of surgical measures undertaken to secure permanent drainage Herman and Feldstein [40] do not consider it proved that any permanent benefit resulted. But possibly this difficulty may be overcome Chronic hydrocephalus is, in the great majority of cases, the result of a past meningitis (Weber, [83] Hildesheim [43]). and for this sequel of cerebro-spinal meningitis Dandy [20] advocates the radical operation of excision of the choroid plexuses of both lateral ventricles in cases in which the internal hydrocephalus is "communicating" —namely, not entirely cut off from the subarachnoid space; in this way the main source of the cerebro-spinal fluid is removed, but the choroid plexus of the third and fourth ventricles will secrete a sufficient amount of fluid.

Treatment with Soamin and Hexamine.

Soamin was first used in cerebro-spinal fever by T. A. Johnston, [45] who in 1910 published two cases that recovered after intravenous injections. Shircore and Ross [78] subsequently gave intramuscular injections of 5 gr. on the first and second days and 3 gr. on the fourth day to 127 cases in British East Africa; of these, 37 died within 60 hours and were regarded as hopeless under any kind of treatment, and of the remaining 90 cases 56, or 62 per cent., recovered. In 1915, when Low [50] again drew attention to its use, soamin was employed intramuscularly in a certain number of cases. In the Navy during that year 21 cases with 7 deaths, or 33 per cent., were treated by soamin alone, and 18 cases with 11 deaths, or 61 per cent., by soamin and intrathecal injections of serum. Comparison of these two series certainly suggests that the intrathecal injection of serum did harm.

During the four years of the war soamin, either alone or in combination with various forms of treatment, was given to 53 naval cases, with a mortality of 23, or 43·4 per cent.; this is higher than the mortality of 30 per cent. among 214 cases treated during the second, third, and fourth years of the war by Flexner's serum either alone or in combination with other brands of serum. Although Batten [4] suggested that it would be safer to employ salvarsan, bad effects, such as optic atrophy, from soamin have not been reported in this disease; one naval case received 42 gr. intramuscularly without any harm. It is unlikely that arsenic compounds would have any effect on meningitis, but conceivably they might do good in the septicæmic stage.

In a few instances antimony tartrate has been given intravenously.

Hexamine, which owes its antiseptic power to the liberation of formaldehyde in an acid solution, has been extensively tried in meningitis on the basis of Crowe's [15] observation that it deferred or prevented experimental streptococcic meningitis. Presslie and Lindsay [68] speak well of it, but in general the clinical results have been most disappointing, and it is obvious that formaldehyde was not likely to be liberated in the cerebro-spinal fluid. Guest and Fairley [24] gave it in large doses by the mouth intravenously, and intrathecally to 20 cases with 80 per cent. mortality, and found that when given by the mouth hexamine and not formaldehyde appeared in the cerebro-spinal fluid. In a similar though short trial of helmitol, which liberates formaldehyde in an alkaline solution, they obtained more encouraging results.

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