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RECENT KNOWLEDGE OF THE INCIDENCE AND CONTROL OF CEREBROSPINAL FEVER*

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Although cerebrospinal fever is a comparatively rare disease, as judged by the standard of many of the common infections, a considerable amount of literature concerning it has appeared during the last twenty years. It is impossible within the scope of the present paper to deal even briefly with all aspects of its control and treatment. Consequently certain subjects are surveyed fairly fully, but others are merely mentioned or are omitted entirely.

Epidemiology

The first classical description of the condition which we now recognize as cerebrospinal fever was given by Vieussieux of Geneva in 1805. There is reason to believe, however, that the disease had appeared at intervals during the preceding 300 years, and references are made in the early literature to outbreaks in Holland, France, and other parts of Europe. In 1661 Willis described a "new disease" in which the pathological features resembled those of cerebrospinal fever. Sydenham also described a "new fever" in 1685; in this cerebral symptoms often followed fever and catarrh, and purple spots were frequently seen on the skin. The history of the disease from 1805 onwards was very fully dealt with by Hirsch (1886), who divided the intervening years into four periods of epidemic prevalence, ending in 1886. To these Sir Humphry Rolleston added a fifth or modern period, starting in 1903 and continuing to the present day. Indeed, it does not seem likely that we are soon to pass out of this period. In the years 1908-10 the disease was epidemic in France, and in 1910 and 1911 large outbreaks were reported from the United States.

In severe epidemics a notable feature of acute cases has often been the presence of a characteristic haemorrhagic rash, made up of small petechiae or, in other cases, more widespread and purpuric. The incidence of rashes varies widely. In an account of an outbreak in 1806-7 North says that they were present in almost every case. During the Great War Sir Humphry Rolleston (1919) found that they occurred in 59 per cent. of cases, and in the same period Worster-Drought and Kennedy (1919) discovered them in 53 per cent. of their cases. In an outbreak of a severe nature reported by me (Underwood, 1932) a rash was seen in 32 per cent. of cases. On the other hand, Borovsky (1930) reported the incidence of rashes as occurring in only 6.7 per cent. of cases in Chicago. Despite

their variability the rashes have given cerebrospinal fever its popular name—"spotted fever." As such it has spread among the public a dread which the high mortality in the past has done little to belie. During the last war "spotted fever" caused many deaths among the civilian and military populations of this and other countries. It was then regarded as a condition associated with the movement of populations and the crowding together of troops in billets. Nevertheless the cessation of hostilities did not lead to a practical extermination of the disease. In recent years epidemics have been widespread and severe in many parts of Europe, in India, and in tropical countries such as the Sudan and other parts of Northern Africa.

Mention should be made here of the supposed association of cerebrospinal fever with certain diseases, especially influenza and other epidemic diseases of the central nervous system. There is much to be said for the views of Hamer (1906, 1928) and of Crookshank (1922, 1930) that outbreaks of these conditions are due to a change in the "epidemic constitution" of the community. Hamer (1917) applied his theory specifically to cerebrospinal fever. For a discussion of certain aspects of the theory in its relation to some of the rare encephalitic complications of infectious fevers reference may be made to a paper by me (Underwood, 1935). It is possible that the present war and the epidemic of cerebrospinal fever may be followed by other epidemiological happenings of great interest.

Incidence in Great Britain

Cerebrospinal fever became notifiable in this country in 1912, and Table I shows the notifications and deaths

TABLE I.—*Cerebrospinal Fever in England and Wales: Cases and Deaths*

Year	Notifications	Deaths	Year	Notifications	Deaths
1913	305	232	1927	469	430
1914	315	396	1928	412	438
1915	2,566	2,203	1929	650	588
1916	1,306	1,368	1930	661	632
1917	1,465	1,651	1931	2,152	1,440
1918	798	926	1932	2,087	1,213
1919	848	694	1933	1,668	942
1920	583	533	1934	1,079	729
1921	411	416	1935	864	617
1922	344	360	1936	967	635
1923	300	284	1937	1,112	698
1924	397	310	1938	1,258	652
1925	402	354	1939	1,508	—
1926	384	365	1940*	5,093	—
			(first 13 weeks)		

* A paper read before the Home Counties Branch of the Society of Medical Officers of Health.

*From Weekly Returns of Registrar-General (corrected).

from 1913 to the present day. The data given are those published officially by the Registrar-General. It should be noted that in many years the deaths exceeded the notifications. This is a caustic commentary on deficiencies in diagnosis and on the non-notification of cases as soon as the diagnosis was established. The deaths for the year 1939 are not yet available officially. The figure 5,093 for notifications for the first thirteen weeks of 1940 is the sum of the corrected notifications given weekly by the Registrar-General for the country as a whole. The notification figures for counties and for administrative areas given in Table II and discussed in the text are uncorrected figures from the Registrar-General's weekly returns.

Cerebrospinal fever first gained notoriety by its prevalence in 1915. In this outbreak the disease was supposed to have been introduced into this country by Canadian troops who were overcrowded on troopships. In Table I the figures include only civilian cases. Some idea of the real extent of the outbreak in that and the following years may be obtained from the statement that while, as the table shows, 6,450 civilian cases occurred in the years 1914-18, during the same period in England and Wales 3,915 Service cases were notified, and that, in addition to civilian deaths shown, 1,753 deaths took place among members of His Majesty's Forces (Reece, 1923).

From the data given in the table it is evident that the present epidemic surpasses in intensity any other outbreak recorded in this country. If it is considered that epidemic prevalence—if such a term can be applied to a condition which produces relatively few cases—began about 1936 or 1937, in duration the outbreak we are at present experiencing bids fair to be one of the most important on record. The table also shows roughly that cerebrospinal fever tends to occur in waves of varying amplitude. In the United States Hedrich (1931) showed that the interval between adjacent crests in different areas varies between six and twelve years, with occasionally intervals of even twenty-five years.

The outbreak of 1931-2 was of a magnitude comparable to that of the war years. It appeared at first that the present outbreak might be of a similar size, but during the first weeks of this year it became apparent that a much bigger epidemiological event was in progress. During the first thirteen weeks of 1940, 5,093 cases were notified—including non-civilian cases—so that it cannot be too strongly emphasized that the present outbreak is easily the largest in the records of this country.

Time Incidence

Table II gives the number of cases notified week by week in England and Wales, in London, and in certain other administrative areas. The weekly incidence of the disease for

the whole of the geographical counties in England and Wales was tabulated, and those counties which showed the largest numbers of cases were chosen for further investigation. Table II deals only with these selected areas. It will be seen that in a period of eight weeks the incidence in the country as a whole increased sixfold. The peak of the epidemic—so far as is known at present—occurred in the week ending March 2, since when there has been a gradual decline. Although there was an increase to 521 cases in the week ending March 30, there was a decline—not shown in the table—to 436 cases in the week ending April 6. The weekly figures of incidence are reproduced for only a few of the counties in which most cases were notified, but it can be taken that in practically all the counties in which the disease was at all prevalent one or more cases had occurred during the week ending January 6. In almost all the counties in which the incidence was high the peak of the outbreak was reached during one or other of the two weeks ending March 2 and March 9 respectively. This suggests that the infection—in contradistinction to a prevalence of the meningeal complications—must have been widespread throughout the country before the close of 1939.

Geographical Distribution

The geographical distribution of the 1931-2 epidemic was dealt with by me in a previous paper (Underwood, 1933). The geographical counties in the order of prevalence of cases—not case rates—were: West Riding of Yorks, 1,358; Northumberland and Durham, 559; London, 421; Lancashire, 383; Notts, 231. It will be noted that all of these are industrial districts, and that there is no suggestion that towns on the coast were highly affected. The distribution of the civilian cases in the Great War epidemic was very different. The civilian mortality in 1915 was 80 per million in the South, 35 in the Midlands, 25 in Wales, and 12 in the North. It is probable that the high incidence in the South was due to the large aggregations of troops in these areas.

The present outbreak is very widespread, and there is no county in England and Wales which has not had at least one case. It is only remote and little-inhabited counties like Rutland, Huntingdon, Isle of Ely, Holland (Lincs), Westmorland, Anglesey, Cardigan, Merioneth, and Montgomery that have had under four cases each. In the thirteen weeks ending March 30 the highest number of cases in any geographical county was 414, in Lancashire. The administrative county of London had 331 cases. According to the actual number of cases recorded in the geographical areas, the counties follow in this order: Glamorgan, 308; Southampton, 294; West Riding of Yorks, 224; Surrey, 211; Warwick, 199; Kent, 194; Essex, 161; Stafford, 150; Monmouth, 145; Somerset, 140; Wiltshire, 133; Gloucester, 131; Middlesex, 121; Berks, 107; Leicester, 104; Durham, 102; Devon, 100. The remaining counties had fewer than 100 cases in the thirteen-week period. (It is worth while noting that the county of Denbigh had 93 cases.) County rates were not calculated, since the figures would be purely provisional and might give a misleading picture of the relative incidence. A feature of the incidence is that the three counties with the largest number of cases are counties

TABLE II.—Notifications of Cerebrospinal Fever by Weeks in Certain Areas

Area	Week ending													Total
	Jan. 6	Jan. 13	Jan. 20	Jan. 27	Feb. 3	Feb. 10	Feb. 17	Feb. 24	Mar. 2	Mar. 9	Mar. 16	Mar. 23	Mar. 30	
England and Wales...	53	107	144	184	299	406	557	585	617	603	541	476	521	5,093
London...	4	5	5	13	24	20	28	27	33	35	51	52	34	331
Lancashire Adm. County	2	1	7	5	7	16	13	11	19	10	14	13	15	133
Liverpool...	4	3	2	3	3	7	13	19	14	13	15	11	8	115
Manchester...	—	2	4	2	1	6	3	4	8	7	8	6	14	65
Glamorgan Adm. County	2	5	11	7	9	24	14	19	19	20	17	17	24	188
Cardiff...	3	—	—	3	4	10	11	6	11	7	10	5	5	75
Swansea...	—	—	3	1	4	1	7	4	6	4	5	3	4	42
Southampton Adm. County	1	3	3	5	14	12	25	26	15	11	12	12	9	148
Portsmouth...	—	1	5	4	5	2	6	5	23	3	—	2	2	58
Southampton...	—	—	1	—	3	6	12	12	9	9	2	3	7	64
Surrey Adm. County	2	5	12	9	10	22	27	21	18	20	22	18	9	195
Yorks W.R. Adm. County	—	—	—	2	8	4	6	5	11	12	9	9	8	74
Sheffield...	—	—	—	2	—	—	3	9	3	11	9	13	7	57
Leeds...	—	—	—	2	—	1	1	3	7	3	6	2	8	33
Bradford...	—	—	—	1	—	—	2	2	2	8	1	4	1	21
Scotland...	18	23	36	46	75	96	114	134	115	105	110	106	95	1,073

bordering the sea. Each of these counties has important ports or centres of military or naval activities. It is most significant that Wiltshire, which is obviously a centre for troops, had 133 cases. Similarly Dorset had 66 cases.

Further analysis of the five counties with the largest number of cases—Glamorgan, Lancashire, Southampton, Surrey, and the West Riding of Yorks—provides further interesting features. In Lancashire the incidence fell most heavily on Liverpool, Manchester, and the urban and rural districts of the administrative county. In all of these administrative areas the epidemic started either in the week ending January 6 or in the week ending January 13. Liverpool had 115 cases, Manchester 65, and 133 were notified in the administrative county. Salford had 22 cases, St. Helens 15, and Bootle 13. The other county boroughs escaped relatively lightly. In Glamorgan, Merthyr Tydfil had only 3 cases, but Cardiff had 75, Swansea 42, and the administrative county 188. Southampton administrative county had 148 cases, Portsmouth 58, and Southampton county borough 64. In the Surrey geographical area the administrative county had 195 cases and the remaining 16 were notified in Croydon.

The position of the West Riding is interesting in that the majority of the cases occurred in the administrative county and in the three largest cities. The administrative county had 74 cases, and Sheffield, Leeds, and Bradford had 57, 33, and 21 cases respectively. It is interesting to note that the three county boroughs which were most heavily involved in the whole of England and Wales in the 1931-2 epidemic—namely, Barnsley, Rotherham, and Doncaster—have each escaped so far with six cases or less.

In summarizing the incidence in England and Wales it should be pointed out that the disease has produced most cases in large industrial cities and in the ports. Scotland has been affected in similar fashion, since, as Table II shows, the general progress of the outbreak has been proportionally the same in Scotland as in England and Wales. The peak of the outbreak was reached in the week ending February 24, when 134 cases were notified, but the decline has so far been more gradual than the rise. Published figures show that the incidence in the large cities has been considerable. In the twelve weeks January 1 to March 30, and excluding the week ending January 20, concerning which data are not available at the moment of writing, 217 cases were notified in Glasgow and 154 in Edinburgh. Details of the position of the notified cases which have occurred in non-civilians in England, Wales, and Scotland are not at present known, but there is reason to believe that this proportion is not nearly as high as might be expected.

Age Incidence

The age incidence in the present epidemic is not known, but casual information which has come to notice suggests that a considerable proportion of the patients are older children and young adults—that is, the ages at which mortality is naturally lowest. In 1917, 12.5 per cent. of the cases occurred in children under 1 year old, 32.1 per cent. in children under 5, and 48.2 per cent. in children under 10 years. In London the corresponding figures were considerably higher. In an epidemic in Columbia in 1936 and 1937 Dauer showed that 68 per cent. of the coloured patients and 42 per cent. of whites were under 20 years old.

Family Infection

Since cerebrospinal fever is a condition essentially associated with overcrowding and bad ventilation it might be thought that multiple cases in households would be common. Such is not the case. There are many classical observations on this point which need not be mentioned. Similarly, recent results confirm these statements. Jimura (1932), in Japan, showed that out of over 1,000 cases family infection occurred very rarely. Husein (1934), in Cairo, found that out of 1,090 cases two occurred in the same house on only twenty-six occasions, and three in the same house on only two occasions. Blackerby and Caudill (1938), in Kentucky, showed that of 290 families in which cases had occurred only 51, or 17.3 per cent., had

multiple cases. Similarly, out of 1,624 cases Appelbaum (1938) found more than one case in a family in thirty-eight instances. At the present time general data on which this factor may be assessed are not available, and figures for my own area are too scanty to warrant quotation. Nevertheless the preliminary inference is that the present outbreak is no exception to the general rule so far as the incidence of family infection is concerned.

Method of Spread

It has long been held that the spread of cerebrospinal fever is essentially due to overcrowding and bad ventilation, and that when under such conditions a new strain of the meningococcus is introduced the non-contact carrier rate increases rapidly. Attempts were made to fix a maximum level for the percentage of carriers among non-contacts, above which cases of cerebrospinal fever would be likely to arise. In barracks and army huts this view was obviously important, and Glover's (1918a, 1918b) classical work on bed-spacing gave apparently satisfactory results.

It is now known that the proportion of the general population of the area who are carriers can vary within wide limits, and a similar variation may be found among actual contacts. For example, Silverthorne and his colleagues (1939), in Toronto, found that out of 327 contacts examined 31 per cent. were positive and that 94 per cent. of these organisms were virulent for mice. In 33 out of 42 families of patients it was found that one or both parents were harbouring the organism. During a period of over four years these workers examined 2,378 swabs, and positive results were obtained in 20 per cent. These authors suggest that the bactericidal power of human blood against the meningococcus, or the ability of strains to survive in human blood, may be as important in assessing the potential pathogenicity of a strain of the meningococcus for man as is an artificial mouse-virulence test. In the Sudan epidemic of 1932 Riding (1932) found that the contact carrier rate was only 6.2 per cent. In a Calcutta epidemic Russell (1936) found that 20 to 30 per cent. of healthy persons were carriers.

The work of Dudley and Brennan (1934) threw considerable doubt on the theory that epidemics of meningococcal meningitis are correlated with high incidence of carriers of the meningococcus. In the investigations of these writers, which extended over a period of nearly two and a half years at Chatham, it was shown that the mean carrier rate among non-contacts was 54 per cent. During this period only eleven cases of cerebrospinal fever occurred, and the carrier rate among contacts varied only from 9.4 to 14.3 per cent. On the theories current during the last war there should have been a large outbreak of cerebrospinal fever at the Chatham establishment. It would appear that the most likely explanation of the spread is that an epidemic is determined by the introduction into the community of an organism which is not only highly virulent but which is possessed in high degree of the power of invading the meninges. But much of this type of work has been done in a closed environment, and it is not always advisable to apply the results to open communities.

Much work has been done in the past on the relation between atmospheric conditions and the onset of cerebrospinal fever. No very definite conclusions have been reached, though it is well known that epidemics are more frequent in the spring. Recent work of Corkill (1939) is worthy of consideration. Working in the Sudan, he concluded that susceptibility to meningococcal meningitis is a deficiency state which is activated by the seasonal

advent of heavy ultra-violet-ray irradiation. According to Corkill the association with rainfall is incidental, and clouds are beneficial in that they reduce ultra-violet irradiation. As applied to northern latitudes this theory would mean that meningitis epidemics occur when the bright sunlight of spring accentuates the vitamin deficiency which has been experienced in the winter.

Mortality

The mortality from cerebrospinal fever varies enormously in different outbreaks. Many classical examples are well known, and the fatality rates in less-known outbreaks are summarized in Table III. The mortality also

TABLE III.—*Cerebrospinal Fever: Mortality in Recent Epidemics*

Year	Source	Cases	Deaths	Fatality per cent.	Area
1939	Longe, Hervé, and Benderitter ..	12	5	41.7	Dahomey
1939	Dauer ..	338	145	42.9	Columbia (Washington)
1939	Silverthorne <i>et al.</i> ..	51	21	41.2	Toronto
1932	Williams ..	85	30	35.3	Sheffield
1932	Pacha ..	3,139	—	41.9	Egypt
1930	Atkey (1932) ..	865	665	76.9	Sudan
1932	Riding ..	4,333	2,239	51.6	Egypt
1926-8	Jimura ..	1,036	—	65.5	Japan
1918	Cadbury ..	1,232	968	78.6	Hong Kong
1929	" ..	1,099	403	36.7	Shanghai
1932	" ..	107	59	55.1	"
1932	" ..	207	122	58.9	Hong Kong
1932	" ..	600	348	58.0	Macao
1930	German figures ..	663	351	52.9	Germany
1931	" ..	574	307	53.5	"
1932	" ..	518	256	49.4	"
1932	" ..	598	280	46.8	"
1934	" ..	1,016	423	41.6	"
1936	Cormack ..	139	75	53.9	Kenya
1936	" ..	102	84	82.4	"
1920-36	" ..	23,685	12,129	51.2	U.S.A. (22 towns)
1929	Branham (1937) ..	10,551	4,787	45.4	U.S.A.
1934	" ..	2,500	1,107	44.3	"
1935	" ..	5,766	2,297	39.8	"
1937	Sorel ..	521	345	66.2	French Niger
1937	" ..	8,653	6,456	74.6	British Nigeria
1937	Van Campenhout (1938) ..	215	119	55.3	Belgian Congo
1936-7	Neff and Markides (1937) ..	800	—	34.0	Cyprus

varies very largely according to the age of the person attacked. In the New York epidemic of 1904-5 the fatality was 73.5 per cent. in about 4,000 cases. A rate of 90 per cent. has been recorded. In the Glasgow 1906 epidemic the rate was 81 per cent., and in the ten-year period 1906-15 the rate in Glasgow was 71.9 per cent. MacNalty (1927) considered that this Glasgow rate was a fair average for the disease in an epidemic period. In recent years it was considered that the fatality was decreasing. Fairly frequent examples of high rates were found, however, in the epidemic of 1931-2. I myself reported such an outbreak in which the mortality was extremely high, despite intensive use of all the therapeutic measures then available (Underwood, 1932). Consideration of other data over a number of years gives strong support to the theory that cerebrospinal fever may be epidemic and highly virulent in one localized area, while in near-by areas the disease may be epidemic but of a more benign type. Few attempts have so far been made to explain these interesting occurrences. During the last two years the advent of chemotherapy has encouraged the belief that the fatality rate in an epidemic period will fall.

Satisfactory figures for the present epidemic are not officially available for large numbers of cases, and in order to gain some idea of the effect of the new therapy throughout the country I made certain inquiries regarding the areas in which most cases have occurred. The registered deaths from cerebrospinal fever were tabulated for these areas week by week. Allowing one week or a portion thereof as the period between notification and death in any case, the fatality rate for each area has been

calculated, using the deaths occurring in the week ending January 13 and the following weeks until the week ending March 30, and the notifications received in the week ending January 6 and in the following weeks until the week ending March 23. On this basis the following are the fatality rates for the different areas: Liverpool, 24.3 per cent.; Manchester, 27.5 per cent.; Cardiff, 14.3 per cent.; Swansea, 21.1 per cent.; Portsmouth, 26.8 per cent.; Southampton, 28.1 per cent.; Surrey County, 14.0 per cent.; Leeds, 32.0 per cent.; London, 28.6 per cent.; West Riding of Yorks, 34.8 per cent. (In the case of London and the West Riding the deaths of non-civilians are not included, so that in these two areas the true fatality rates may be slightly higher than the rates given. In the other areas mentioned deaths of non-civilians are included, but actually these Service deaths were few.) The case mortality rate for these areas taken together—based on 216 deaths in 901 cases—is 24.0 per cent., which presumably represents the average figure for the country as a whole. It should, however, be mentioned that the fatality rate based on 978 cases occurring in Scotland during the corresponding period is only 8.9 per cent. If the figures for Scotland are included with the selected figures for England and Wales the combined fatality rate is reduced to 16.1 per cent. It should be said that these figures are extremely satisfactory, and that they mark a very distinct advance on anything previously experienced in connexion with the fatality from this serious disease.

The particularly interesting feature of these rates is the fact that they are uniformly low, when considered in the light of all previously accepted figures for the mortality from this disease. Although the West Riding rate of 34.8 per cent. is based on a small number of cases, there may be a suggestion here that the organism is more virulent in Yorkshire than in certain other parts of the country. This suggestion receives some confirmation from the fact that the Leeds fatality rate is 32 per cent. It is perhaps the case that the particular strain of the organism which is prevalent in the West Riding is especially virulent, as in the 1931-2 epidemic.

Prophylaxis

The prophylaxis of the disease is very adequately dealt with in the recent circular issued by the Ministry of Health. If it is true that the fatality can be reduced to an approximate level of 20 per cent. or less, then more active measures are certainly not advisable. Nevertheless, I do not think that experiments on active immunization should be completely discouraged, since at any time a resistant strain of the organism may be introduced into the community. In the Colonies the need for a satisfactory method of active immunization has long been apparent.

Such a method was first tried by Davis in 1907. In 1917 Greenwood discussed the results of inoculation of over 4,000 persons with a polyvalent vaccine in Salisbury, and he made out a *prima facie* case in favour of prophylactic inoculation. In 1923 Calbairac used two injections of a vaccine prepared from local strains. Riding and Corkill (1932) carried out an extensive experiment in 1931. In all 10,000 persons were vaccinated and the experiment was carefully controlled. There was, however, no appreciable difference in the incidence in the two groups. In 1933 Ismail reported on the vaccination of 74,000 persons in Turkey, but again the results were not conclusive. In 1935, in India, Russell (1936) vaccinated two series of persons during a large epidemic in a prison containing 2,004 people. Half the population were inoculated and the other half were used as controls. There were no cases in either group. In a Borstal insti-

tution 766 persons were inoculated and a similar number were used as controls. No cases occurred among the vaccinated persons, but there were six cases in the controls. Pergher and Portois (1936) vaccinated 120,000 persons with vaccine prepared from local strains. There were no cases among the vaccinated population. Saleun and Ceccaldi commented on their vaccination experiments in 1936, but the figures given are not complete. In 1938 Kuhns and his colleagues (1938) carried out interesting experiments in certain camps in the United States. They used a filtrate of the meningococcus for skin-testing and later for immunization. The testing was found to be hardly worth while, and at a later date all persons were immunized regardless of their reaction to the intradermal tests. These authors give an interesting table, but there is no evidence that the prophylactic treatment actually had any effect on the incidence of the disease in the camps. Sorel (1937, 1938), in Africa, inoculated about 5,000 persons, none of whom contracted the disease. Some cases occurred among the controls, but the number of these controls is not adequately stated. The most recent experiment on this subject was carried out by Maclean and Bevan in Cyprus in 1936-7. Unfortunately this careful experiment began during a waning epidemic and the results are therefore inconclusive.

It is not sufficiently realized that, in assessing the value of experiments of this type, it is fundamental that certain conditions should be satisfied. (a) The experiment must be adequately controlled and the number of control individuals stated. (b) The control individuals should be drawn from the same population as the inoculated individuals, the age grouping should be approximately the same in the two series, and no selection should be exercised in determining which individuals receive the treatment and which do not. (c) Inoculated and controls must be exposed equally to infection. (d) Infection should be sufficiently widespread to ensure that a significant number of controls actually contract the disease after exposure.

Maclean and Bevan (1939) give a table showing a few details of many of the previous experiments on prophylactic inoculation against cerebrospinal fever. I carefully perused the original papers dealing with these experiments, but in certain instances was unable to confirm the figures given for control groups. It would appear also that the total figures in the table referred to are somewhat excessive, since the experiment recorded by Russell was probably that reported previously by Yacob (1935). Further, it seems very probable that the experiment mentioned by Le Bourdellès and Sédallian (1930) is that previously described by Bruynoghe and Walravens (1926). Particular attention was paid to the four conditions

enumerated above, and those experiments which did not conform to the conditions were discarded. To the data which remained tests of association were applied, and the results are summarized in Table IV.

A χ^2 value of 3.841 means that a difference as great as that actually observed between the two sets of observations would be likely to occur by chance alone in 5 per cent. of an infinitely large number of trials on the scale reported. Similarly, a χ^2 value of 6.635 or over means that a difference as great as that actually found would be expected to occur by chance in only 1 per cent. or less of such trials, if repeated tests of the same magnitude were carried out. Where, therefore, a χ^2 value between 3.841 and 6.635 was observed the difference between inoculated and uninoculated was taken as being unlikely to have arisen by chance alone. Where the χ^2 value is over 6.635 the corresponding difference was regarded as undoubtedly significant.

Excluding the combined observations of Bruynoghe and Walravens, and the original figures of Riding and Corkill, we are left with eight series of observations in Table IV. In two of these eight series there is therefore some evidence that chance alone could not have caused the difference in the incidence of cerebrospinal fever in the inoculated and in the control groups respectively. If environment and exposure to infection were really equal in the corresponding groups the inference is that the real differences in incidence were due to the effects of the inoculations. It may therefore be suggested that the case for prophylactic inoculation in cerebrospinal fever is still very much *sub judice*, though possibly rather stronger than it was when Professor Greenwood examined the problem over twenty years ago. It is certain that the further investigation of the question is a matter for carefully controlled investigations. It is certain also that the time is still far distant when the individual practitioner will be able to consider prophylactic inoculation as a method of dealing with contacts.

Turning for a moment to the immediately practicable aspects of prevention, reference should be made to the vast changes in environmental and social conditions which have been brought about by the war. Evacuation has led to the development of complex changes affecting the normal host-parasite relationship. It is a suggestive fact that most of the counties which are now suffering most heavily from the prevalence of cerebrospinal fever are either within easy travelling distance of a great city or themselves contain such a city within their boundaries. Overcrowding in billets must be guarded against, and in the case, for example, of voluntary evacuation to the houses of friends it is desirable that children should not be sent needlessly from one reception area to another.

The war has also led directly to the congregation in schools and halls of large parties of men and women engaged on civil defence duties. The Home Office A.R.P. Circular No. 134 suggests 14 square feet per man as a suitable standard for superficial area in new buildings erected for the billeting of such personnel. Such a standard is obviously likely to encourage the spread of droplet infection. I have long been aware of the dangers associated with the billeting of these parties. In order to minimize the risk, at the end of February I recommended the A.R.P. controller of the area to agree to the granting of a concession to members of the casualty service personnel. It was recommended that one-third of the men should leave their depots at 10 p.m., sleep in their homes, and return to duty at 8 o'clock the following morning. The men chosen must all live within easy distance of their depots, and they must report

TABLE IV.—Cerebrospinal Fever: Inoculation Experiments

Reference and Area	Inoculated Persons		Controls		χ^2	n	P
	Not Attacked	Attacked	Not Attacked	Attacked			
Bruynoghe and Walravens:							
(a) Etoile-Ruashi ..	877	0	2,658	16	4.02	1	0.04
(b) Panda-Likasi ..	1,113	0	4,027	2	0.01	1	0.92
(c) Kakontwe ..	380	0	811	3	0.32	1	0.57
(d) Kambove ..	634	0	350	0	—	—	—
(a), (b), (c), (d) ..	3,004	0	7,846	21	4.35	4	>0.29
Russell:							
(a) Prison ..	1,002	0	1,002	0	—	—	—
(b) Borstal ..	766	0	760	6	4.18	1	0.04
Zruneck and Feierabend (1931)	22,175	5	19,678	6	0.00	1	1.00
Riding and Corkill:							
(a) Original figures	10,189	9	10,120	13	0.43	1	0.51
(b) Emended figures	10,189	9	18,153	34	3.58	1	0.06

In this table Yates's correction was used in computing the χ^2 values.

immediately should an air raid occur. The total number of men affected is about 900, and the arrangement is still in force. So far no case of meningococcal infection has been found among the personnel. There is of course no proof that the arrangements made did produce this result. A further difficulty directly attributable to the war is that of ensuring sufficient ventilation in buildings during the "black-out." This difficulty is especially marked in depots used for the billeting of civil defence personnel. These buildings do not always have an efficient system of artificial ventilation, and natural ventilation by windows and doors has to be employed. It is possible to provide a satisfactory type of blind or curtain. The windows should always be opened wide after "lights out."

Treatment

The treatment of the disease by polyvalent and by monovalent serum has been sufficiently discussed in the past. Ferry's meningococcus antitoxin has been less used, and it need not be dealt with here. It should be mentioned, however, that, despite the relative success which followed the use of serum in large doses in many areas, outbreaks occurred in which there was doubt whether the serum was as efficient as it should be. For example, Cadbury (1934), in China, stated that the serum was not of much use, and the opinion of those who were in charge of the patients was that lumbar puncture was more effective. At Anhwei there was a mortality of 40 per cent. for untreated cases and 5 per cent. when lumbar puncture alone was employed. Walsh in 1938 reviewed 23,685 American cases occurring between 1920 and 1936. He concluded that there was no evidence that the use of serum had lowered the fatality in recent years. Sorel, dealing with the epidemic in French Niger in 1937, stated that when the treatment consisted of serum together with fixation abscesses 50 per cent. of the patients died. In one province where the treatment consisted only of lumbar puncture together with fixation abscesses, only 9 deaths occurred in 59 cases.

Chemotherapy appears to have been used first by Zeller, Riecke, and Krause, who employed prontosil in 1935. (I have been unable to confirm this reference.) Buttle, Gray, and Stephenson (1936), and later Proom (1937), showed that *p*-aminobenzenesulphonamide would confer on mice a certain degree of protection against the meningococcus. In 1937 Schwentker, Gelman, and Long used such a drug in 10 cases with one death. In 1936 Roche and McSweeney were using a prontosil compound in Dublin, and thereafter case reports became fairly numerous. For example, Willien reported 5 cases (all cured) in 1938. In 1938 Smith, Maxson, and Murphey analysed 157 cases. They found that the fatality was much lower—about 25 per cent.—when serum was not injected to the theca; treatment by intravenous antitoxin with sulphanilamide gave a fatality rate of 12.5 per cent. Sprockhoff reported 15 cases with two deaths in 1939, and Osborn (1939) of Birmingham employed sulphapyridine (M & B 693) with daily lumbar puncture in 3 cases, all of which recovered. Schaefer (1939) treated 17 cases with uleron by mouth together with lumbar puncture; there was a fatality rate of 64.7 per cent. (not 61 per cent., as stated in Schaefer's paper).

Two important communications appeared a year ago dealing with work carried out in the Sudan. Somers (1939) stated that during the years 1934–8 there had been 21,599 cases in the Sudan, with 14,816 deaths. He treated 143 consecutive cases with small doses of sulphapyridine. The fatality rate was reduced to 10 per cent. In all the cases the drug was administered intrathecally, and in most cases also by another route. Bryant and Fairman (1939) treated 21 cases with prontosil and tablets of sulphanilamide; there was one death. They later used sulphapyridine administered intramuscularly. In the whole series of 168 cases there were only 8 deaths—a fatality rate of 5 per cent.

Roche and McSweeney reported the results of their work in Dublin. In 1935–6 they were using the accepted methods of serum treatment; the fatality rate was 75.0 per cent.

Between 1936 and 1938 they used prontosil or soluseptasine in addition, and the fatality rate in 56 cases was 57.14 per cent. In 1938 and 1939 they used only sulphapyridine orally, and the fatality rate was reduced to 7.14 per cent. in 14 cases.

The most important work which has been done on the subject in this country is that of Banks, and anyone who has to treat cases of the disease should refer to his original papers (Banks, 1939, 1940). The recent Memorandum of the Ministry of Health gives an excellent summary of the present position, based largely on Banks's views. The technique of treatment by this method will therefore not be discussed here. Excluding untreated or inadequately treated cases, Banks had only one death in 80 consecutive cases of cerebrospinal fever treated by chemotherapy alone. Emphasis is placed on the necessity for adopting a high initial dosage and for giving subsequent doses according to a prescribed scale, depending on the age of the patient. The oral route can often be employed throughout the illness, but occasionally resort has to be made to intramuscular injection of the sodium salt of sulphapyridine.

Through the courtesy of the medical superintendents of the hospitals for which I am responsible, information regarding the treatment of 50 cases of cerebrospinal fever was collected. The results are given in Table V. From this table it will

TABLE V

Method of Treatment	Cases	Deaths	Fatality Rate per cent.
Serum alone	27	19	70.4
Serum and sulphanilamide	6	3	66
Sulphanilamide (alone or with drugs)	3	3	
Serum and sulphapyridine	2	—	7.1
Sulphapyridine alone	12	1	

be seen that with serum alone the fatality approximates to the rate which is commonly found during epidemic periods, but is rather high for sporadic cases. Treatment by means of sulphonamide preparations—with the exception of sulphapyridine—was very disappointing. The prontosil used was mainly the album variety, but in a few cases prontosil rubrum solution was injected intrathecally. There was no significant difference between these results and those obtained by serum treatment alone. On the other hand, treatment by sulphapyridine gave eminently satisfactory results—especially in view of the fact that most of these patients were treated during the present outbreak. The ages of the patients ranged from under 1 year to 76 years. Twenty were aged 5 years or under, so that in general the age grouping was unfavourable to a high recovery rate. No useful purpose would be served by giving details of the age grouping in this small series, but it may be said that five of the patients who had sulphapyridine were aged 5 years or under. The patient in this group who died was 2 years old.

There is obviously a very significant difference between the results obtained in the sulphapyridine series on the one hand and in the serum and sulphanilamide series on the other. There is, however, no significant difference between the results obtained in the serum and the sulphanilamide groups. It may be suggested that if the dosage of sulphanilamide had been higher the results would have been better. This may be so, but it should be noted that the figures for sulphanilamide do not differ very largely from those obtained by Roche and McSweeney. One feels inclined to doubt the efficacy of sulphanilamide against certain strains of the organism. The reports of this series of cases confirm the fact that chemotherapy materially shortens the duration of the illness (the shortest period of recovery in hospital was twenty days) and hastens the clearing of the cerebrospinal fluid.

General Remarks

The present wide-spread outbreak of cerebrospinal fever has given unrivalled opportunities for the testing of chemotherapy, and the results so far obtained have been extremely encouraging. Nevertheless, I am of the opinion that the prevailing strain of the organism is not as virulent as was the case in some previous epidemics, or that the factors which make for virulence are not present to

the same degree. One would like to be certain of the effects of chemotherapy in an explosive outbreak of cerebrospinal fever occurring in a circumscribed area. The time factor in the host-parasite relationship must also be taken into account, and a considerable period must therefore elapse before a final conclusion can be reached.

In the matter of prevention any measures which are liable to minimize the overcrowding, bad ventilation, and gross dispersal of individuals occasioned by the war should be encouraged. Prophylactic inoculation is still an experimental problem, and no useful purpose would appear to be served by its employment in this country. In the treatment of carriers there would seem to be opportunities for further investigation regarding the effects of chemotherapy.

Summary

The epidemiology of cerebrospinal fever is discussed in relation to the present outbreak. During the first thirteen weeks of the year 5,093 cases were notified in England and Wales. This figure exceeds the total notifications in the years 1915, 1916, and 1917 taken together. The peak of the outbreak occurred in the week ending March 2; the decline has been slow and interrupted.

Analysis of the geographical distribution showed that every county was affected. Most cases were notified in Lancashire, London, Glamorgan, Southampton County, the West Riding, and Surrey—in that order. Areas especially affected were the large industrial cities, the ports, and the reception areas. Scotland was affected similarly.

From data covering a large population it is estimated that the average fatality rate in the present epidemic is 24.0 per cent., though there is considerable variation between different areas. The fatality in Scotland is lower.

The history of inoculation against cerebrospinal fever is reviewed. Many of the recorded experiments do not permit of further investigation. A statistical analysis of eight series of observations is given, and it is shown that in only two of the eight could it be said that chance alone could not have caused the difference in the incidence of cerebrospinal fever in the inoculated and in the control groups respectively. The value of this method of prevention is still *sub judice*. Such experiments should satisfy certain necessary conditions.

Practical measures of prevention are discussed. Emphasis is placed on the practicability of reducing the density of population in A.R.P. depots at night. Adequate ventilation in the "black-out" is essential.

The literature of chemotherapy in cerebrospinal fever is briefly reviewed. In a small series of cases it was found that with sulphapyridine the fatality was 7 per cent., whereas with serum or sulphanilamide it was over 60 per cent. There was thus a significant difference between the results obtained with sulphanilamide and with sulphapyridine respectively. Though the sample is small, the results are similar to certain other published figures.

I am indebted to the medical officers of health of the administrative areas mentioned in the text for their kindness in supplying me with certain figures regarding deaths in their areas. I have also to thank my colleagues, Mr. O. R. M. Kelly, F.R.C.S., Dr. Donald MacIntyre, and Dr. B. Rivers-Pitt, for supplying me with the case sheets of the local cases, and for other assistance.

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The congress of 550 students which met at Leeds recently, and which was organized by the National Union of Students, considered through one of its commissions the relation between medical problems and modern social conditions. The difficulties of the medical profession were considered to be insuperable under existing social conditions; only by a fundamental alteration in the condition of life of the population could there be any great reduction in the high incidence of tuberculosis, venereal diseases, and rheumatic diseases affecting the heart, etc. A resolution was passed by 448 votes to 1 urging the need for a unified and comprehensive system of free health services. As an immediate step national health insurance should be extended to include dependants and old age pensioners. Later in the congress forty medical students from medical schools in England and Scotland discussed some general problems. There was a feeling of isolation of the medical students from the rest of the student body, and an appeal was made for closer and more friendly student co-operation. The inertia of medical students was felt by many to be due to the "faculty management of medical societies." As regards the curriculum opinion was divided between removal of some of the scientific subjects and minor changes only. It was considered that many of the faults might be overcome by a closer relation of anatomy and physiology to clinical practice. Non-medical courses directed to broadening the cultural background were urged, as also were experience of general practice, training in psychology, and a compulsory year of internship before final qualification.