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by Sir Humphry Rolleston.**

Contributors

Rolleston, Humphry Davy, Sir, 1862-1944.

Publication/Creation

[Place of publication not identified] : [publisher not identified], [1919?]

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Cerebro-spinal Fever in the Royal Navy (August 1st, 1917—July 31st, 1918)


BY

Temporary Surgeon Rear Admiral Sir HUMPHRY ROLLESTON

K.C.B., M.D., F.R.C.P., R.N.

*Consulting Physician to the Royal Navy;
Emeritus Physician, St. George's Hospital*

[Reprinted from "Journal of the Royal Naval Medical Service," 1919,
Vol. V., pp. 131-141.]



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CASES OF CEREBROSPINAL FEVER IN THE ROYAL NAVY. AUGUST 1, 1917—JULY 31, 1918.

BY TEMPORARY SURGEON REAR-ADMIRAL SIR HUMPHRY ROLLESTON,
K.C.B., M.D., F.R.C.P.

As in the last report, the total number of cases occurring since the outbreak of hostilities have been analysed as far as is necessary for comparison with those in the fourth year of the war. The present report contains:—

- (1) Remarks on the incidence of the cases.
- (2) Remarks on some clinical aspects.
- (3) A summary of the results of treatment.

(1) INCIDENCE OF THE CASES.

During the year August 1, 1917, to July 31, 1918, there were 92 bacteriologically proved cases of cerebrospinal fever as compared with 143 during the third, 104 during the second, and 170 during the first year of the war, the percentages for the first, second, third, and fourth years being 33·4, 20·4, 28, and 18 of the total 509 cases. Except for the rise in the third year of the war, which, as mentioned in the last report, coincided with a rise in the number of cases in the civilian and military populations, and also with an increased percentage of carriers in the Navy, there has been a fall during the years of the war although the personnel of the Service has steadily increased. While the satisfactory result may be correlated with the vigorous prophylactic measures, it cannot be agreed, as Dr. Addison¹ is reported to have said, that it was thus stamped out in a year.

Out of the 92 cases the large depots at Plymouth (36), Portsmouth (17),

¹ Addison, C., *Observer*, January 12, 1919.

the Crystal Palace (15), and Chatham (6), provided 74, or 80 per cent. Out of the 509 cases of cerebrospinal fever in the Navy from the beginning of the war up to July 31, 1918, 384, or 75 per cent., arose in the large depots at Plymouth (130), Portsmouth (127), Crystal Palace (74), and Chatham (55), while 59, or 11·5 per cent., arose in sea-going ships. No case of bacteriologically proved meningococcic meningitis occurred at Osborne or Dartmouth during the war.

The monthly incidence, with the results, is shown below:—

			Cases		Deaths		Recoveries
1917	August	...	1	...	0	...	1
	September	...	3	...	0	...	3
	October	...	1	...	0	...	1
	November	...	2	...	2	...	0
	December	...	2	...	2	...	0
1918	January	...	16	...	8	...	8
	February	...	9	...	4	...	5
	March	...	18	...	6	...	12
	April	...	11	...	5	...	6
	May	...	14	...	4	...	10
	June	...	7	...	0	...	7
	July	...	8	...	3	...	5
			92	...	34	...	58

Out of the 92 cases 55, or 60 per cent., occurred during the first four months of 1918, and out of the 509 cases occurring during the first four years of the war 354, or 69·5 per cent., arose during the first four months of the year.

MONTHLY INCIDENCE AND MORTALITY DURING THE FOUR YEARS OF THE WAR.

	Cases					Mortality				
	1914-15	1915-16	1916-17	1917-18	Total	1914-15	1915-16	1916-17	1918-19	Total
August ...	0	4	3	1	8	0	2	1	0	3
September	0	4	5	3	12	0	3	1	0	4
October ...	0	3	3	1	7	0	1	1	0	2
November	1	6	6	2	15	0	5	3	2	10
December	2	8	14	2	26	1	4	7	2	14
January...	27	8	30	16	81	16	3	13	8	40
February	60	26	22	9	117	35	7	7	4	53
March ...	35	20	27	18	100	15	6	7	6	34
April ...	24	7	13	11	55	8	2	5	5	20
May ...	12	7	11	14	44	8	0	4	4	16
June ...	6	3	5	7	21	4	2	1	0	7
July ...	3	8	4	8	23	3	2	2	3	10
	170	104	143	92	509	90	37	52	34	213

Out of the 92 cases 8, or 8·6 per cent., proved fatal within forty-eight hours of the onset; of these fulminating cases 5 occurred in May and 1 each in January, February, and March, thus not conforming to rule that

they chiefly occur at the commencement of an epidemic. In the third year of the war 12 of the 18 fulminating cases occurred before February.

Age Incidence.—Out of the 92 cases 63, or 67·8 per cent., were under 20 years of age (73, or 79·3 per cent., being under 25 years of age), and the number of cases progressively diminished in the succeeding decades. The average age of the 92 cases was 21·3 years, of the 34 fatal cases 19·7 years, and of the 58 recoveries 21·2 years. The extremes of age were 15 and 46 years.

Age periods	Number of cases and percentage of total 92 cases		Deaths and percentage on the age periods
15 to 19	...	63 or 68·5 per cent.	20 or 31·7 per cent.
20 „ 29	...	17 „ 18·5 „	10 „ 58·8 „
30 „ 39	...	8 „ 8·5 „	3 „ 37·5 „
40 „ 49	...	4 „ 4·3 „	1 „ 25·0 „

The mortality in the age periods for the 509 cases for the four years of the war is given for comparison:—

Age periods	Number of cases and percentage of total 509 cases		Deaths and percentage on the age periods
15 to 19	...	328 or 65 per cent. ¹	121 or 37·0 per cent.
20 „ 29	...	117 „ 23 „	59 „ 50·3 „
30 „ 39	...	38 „ 7 „	18 „ 47·3 „
40 „ 49	...	21 „ 4 „	12 „ 57·0 „
50 „ 59	...	5 „ 1 „	3 „ 60·0 „

¹ Seventy-five of these, with twenty-nine deaths, or 38·7 per cent., occurred in the boy training establishments: “Impregnable,” “Powerful,” and Shotley Barracks.

Mortality.—Out of the 92 cases 34, or 37·95 per cent., proved fatal, as compared with 36·2 per cent. in the third, 35·6 per cent. in the second, and 52·9 per cent. in the first year of the war. Among 509 cases of cerebro-spinal fever in the first four years of the war there have been 213 deaths, or 41·8 per cent., of which 146, or 68 per cent., occurred in the first four months of the year.

Day of Death.—Three cases were fatal on the first day, 5 on the second, 1 on the third, 4 on the fourth, 1 on the fifth, 3 on the sixth, and 2 on the seventh, or 19 (55 per cent. of the 34 deaths) during the first week; there were 10 deaths during the second week, 2 in the third, 1 in the fifth, 1 in the seventh, and 1 on the ninetieth day of the disease.

Ranks and Ratings.—There were 4 officers: a Lieutenant (fatal), a Midshipman (recovery), a Paymaster Commander (recovery), and a Chaplain (recovery). The 88 ratings were: Seamen 41 (17 deaths), Boys (seamen class) 11 (4 deaths), Stokers 11 (5 deaths), Marines 5 (4 deaths), Royal Naval Air Service Mechanics 4 (all recoveries), Boy Mechanics 3 (all recoveries), Engine-room Artificers 2 (1 death), Sick Berth Staff 2 (both recoveries), Trimmers 2 (both recoveries), Ship's Steward 1 (recovery), Officers' Steward 1 (recovery), Motorboat Mechanic 1 (fatal), Wireman 1 (recovery), Carpenter 1 (recovery), Bugler 1 (recovery), Writer 1 (recovery).

(2) REMARKS ON SOME CLINICAL ASPECTS.

Onset.—Reference here will only be made to some unusual forms of onset. In three instances (2 fatal) the onset was wildly maniacal. In 5 cases (1 fatal) the onset was marked by abdominal pain, in one suggesting appendicitis, and in another—a bugler aged 15 years—the onset imitated purpura with abdominal symptoms (Henoch's purpura); in 6 other cases (3 fatal) diarrhoea was a prominent feature. In 2 instances joint pains preceded other symptoms and suggested rheumatism. In 7 instances there was acute bronchitis, but only 2 of these proved fatal as compared with 5 cases (5 deaths) of bronchitis or broncho-pneumonia supervening later in the course of the disease. In one case the first indication of illness was syncope. In 27 cases out of the 92, or 29·3 per cent., the disease began within three weeks of joining the Service, and in one of these it followed four days of sea sickness during the first week in the Navy. Out of these 27 cases 10, or 37 per cent., proved fatal, or practically the same mortality as that (37·9 per cent.) of the 92 cases.

Rashes other than herpes occurred in 57, or 62 per cent., of the 92 cases, being characteristically hæmorrhagic in 42, resembling rose spots in 6, and erythematous, macular, or blotchy in 9. The latter may become hæmorrhagic or remain unchanged; but when the further development followed, the entry has been made under the later stage only. In two cases bullæ appeared on the lower extremities; in 1, in which no previous rash was noted, a bulla appeared on the left calf on the third day, followed on the sixth day when death occurred by bullæ on both feet. In the other case, in which there was a well-marked rash, bullæ appeared on the feet on the sixth day and gave a pure culture of meningococci. Out of the 57 cases 24, or 42 per cent., proved fatal, as compared with 28·6 per cent. among the remaining 35 cases, and 37 per cent. mortality among the 92 cases. As would naturally be expected the mortality was higher among the 42 hæmorrhagic cases (45 per cent.) than among the 15 non-hæmorrhagic cases (33 per cent.). The fulminating cases are specially prone to large purpuric patches, and of the 8 cases fatal within forty-eight hours of the onset 6 had a hæmorrhagic rash. Among 502¹ cases of cerebrospinal fever during the first four years of the war rashes were noted in 296, or 59 per cent., with a mortality of 129, or 43·5 per cent.; whereas among the 206 cases without recorded rash the mortality was 80, or 39 per cent. The occurrence of a rash without further qualification is not therefore of bad prognosis, and a distinction in this respect should be drawn between hæmorrhagic rashes, especially the large extravasations seen in fulminating cases, on the one hand, and the non-hæmorrhagic rashes on the other hand. Among 339 cases of cerebrospinal fever during the second, third, and

¹ The discrepancy between 509 and 502 is due to the fact that the notes of 7 cases of the 170 in 1914-15 were not sufficiently complete to allow analysis of most of the symptoms to be made.

fourth years of the war there were hæmorrhagic rashes (purpuric and petechial) in 153 with a mortality of 65, or 42·5 per cent., whereas among 42 non-hæmorrhagic cases there were 12, or 28·6 per cent., deaths.

Other Hæmorrhages.—In 2 cases (1 fatal) sub-conjunctival hæmorrhages were associated with purpura. Out of 339 cases in the second, third, and fourth years of the war sub-conjunctival hæmorrhages occurred in 6. In 1 case (recovery) hæmaturia lasting six days began on the first day of the illness and was associated with a petechial eruption. Among the 502 cases hæmaturia was noted in 4 cases only. Epistaxis occurred in 3 cases, on the fifth (fatal), sixth, and ninth days of the disease; in 1 case there was no rash and in the other 2 the rash had practically disappeared when the epistaxis occurred.

Herpes labialis was noted in 26, or 28·3 per cent. of the 92 cases; in one instance both external ears were involved. It occurred most often on the fourth (9 cases), sixth (7 cases), and fifth (6 cases) days of the disease. In 1 case it appeared on the ninth, in 2 on second day, and in 1 on the third day of the disease. In 17 cases there was also an initial rash due to the disease, which always preceded the herpes. Five cases with herpes subsequently had a serum rash, and in 11 cases an initial rash, herpes, and a serum rash all occurred. Of the 26 cases, 8 or 30·7 per cent., proved fatal. None of the 8 fulminating cases, fatal within the first forty-eight hours of the disease, had herpes, thus contrasting with their association with cutaneous hæmorrhages, and of the remaining 12 cases fatal before the end of the first week herpes occurred in 3 or in about the same percentage as in the whole 92 cases. Out of the 502 cases during the first four years of the war herpes was noted in 117 or 23·3 per cent., being much less frequent than the other cutaneous rashes which occurred in 59 per cent. of the 502 cases. The mortality among the 82 cases of herpes during the second, third, and fourth years of the war was 17, or 21 per cent., as compared with 123, or 36 per cent., among the 339 cases of cerebrospinal fever in these years. The good prognosis formerly ascribed to herpes labialis in cerebrospinal fever probably depends on the fact that a considerable number of cases die before the time at which it appears. Out of 86 fatal cases among 235 cases of cerebrospinal fever in the Navy in the third and fourth years of the war, 27 or almost a third proved fatal before the fourth day of the disease or the period when herpes commonly appears.

Rarer Manifestations and Complications.—Ocular symptoms: photophobia, usually on the second day of the disease, was noted in 8 cases, none of which were stated to have general hyperæsthesia. Ballantyne¹ has never seen true photophobia, and says that blepharospasm, which is commonly associated with general hyperæsthesia, is commonly described as photophobia. Out of 502 cases during four years of war, 52, or 10 per cent., had photophobia. The pupils were reported as unequal in 5 cases, 4 of which proved fatal.

¹ Ballantyne, A. J., *Brit. Med. Journ.*, 1907, vol. ii, p. 190.

Conjunctivitis was reported in 4 cases on the first, second, fourth and fifth days of the disease. It was noted in 28, or 5.6 per cent., out of 502 cases. Panophthalmitis occurred in 2 cases; in 1 case it was double and began on the eighth day of the disease, in the other it was unilateral (R.) and began on the fourth day. Among the 502 cases destruction of the eye occurred in 7 cases, or 1.4 per cent.; it was bilateral in 2, and on the right side in the remaining 5. This fits in with Netter's opinion that the side on which unilateral panophthalmitis occurs is determined by the position, right or left, of the patient's head. Strabismus was noted in 17 (8 deaths), being transient in several. Out of the 502 cases, 59, or 11.7 per cent., had strabismus, and of these 31, or 52.5 per cent., proved fatal. Ptosis was observed in 3 cases (2 fatal); out of the 502 cases 18, or 3.6 per cent., had ptosis, and of these 13, or 72 per cent., were fatal. The mortality is thus 20 per cent. higher than among the cases showing strabismus, and this may probably be correlated with the frequency with which squint is spasmodic rather than paralytic, and with the paralytic origin of ptosis. Nystagmus was reported in 1 case only. Out of the 502 cases nystagmus was noted in 12, or 2.4 per cent. Optic neuritis was reported in 1 case (recovery), but few eases were examined.

Nervous Symptoms.—Paraplegia with vesical symptoms, absent knee-jerks, and altered sensation came on late in 1 chronic case, which had fourteen lumbar punctures and received 240 c.c. of serum intrathecally; presumably this was due to matting together of organizing lymph around the lower part of the cord. Herrick¹ states that chronic or subacute caudal myelitis is common in convalescents as the result of injury by the needle, irritation of the serum, or local meningococcic infection; and quotes a case in which the cauda equina was found to be matted together by hæmorrhagic fibrino-purulent exudation. This case, however, is the only one that has occurred in the Navy during the war. Paralysis of the tongue was prominent in 1 case that recovered. Dysphagia was noted in 3 instances (2 fatal); among the 339 cases during the second, third and fourth years of the war 8 cases of dysphagia with 5 deaths were reported, but this symptom may easily escape observation when the patient is very ill. The knee-jerks were absent in 9 cases (5 fatal); the plantar response was extensor in 10 (4 fatal), and the abdominal reflex noted to be absent in 8 (1 fatal). No special significance appears to be attached to these changes in the reflexes. Definite hysterical symptoms occurred during the course of the disease in 2 cases. General hyperæsthesia was recorded in 5 cases only, and nerve deafness in 5 cases; among the 502 cases deafness was noted in 26, or 5.2 per cent.

Other Clinical Features.—Bronchitis, or broncho-pneumonia, supervened in the course of the disease in 5 cases, with 4 deaths. Pleurisy occurred in 1 case (recovery); pleurisy may, of course, accompany pneumonia or

¹ Herrick, W. W., *Journ. Amer. Med. Assoc.*, Chicago, 1918, vol. lxxi, p. 614.

broncho-pneumonia in cerebrospinal fever, but it may occur without any obvious lung lesion; this was noted in 3 out of the 502 naval cases. Herrick has described meningococcic pleurisy.

A mitral murmur was heard in 5 cases, which all recovered. Albuminuria was noted in 6 cases, 1 of which, with a specific gravity of the urine of 1040, proved fatal. Hæmaturia lasting for six days and appearing with the petechial rash occurred in 1 case (recovery). Among the 502 cases it was noted in 4 (2 fatal), and was contemporaneous with a petechial rash in 3, and due to ascending pyelitis in 1. Otorrhœa on the sixteenth and thirtieth days of the disease occurred in 2 cases (recoveries), and in one instance the disease began with acute otitis, and death occurred on the thirteenth day with a secondary pneumococcic infection of the cerebrospinal fluid. Among 502 cases otitis occurred in 10. Furunculosis at the end of the third week of the disease complicated 4 cases. Synovitis was noted in 4 cases (1 fatal), on the fifth, sixth and seventh days of the disease, affecting the knee (3), wrists (2), and ankles (1); in one instance only was a single joint (knee) affected. All the cases had a hæmorrhagic rash, but in none was there iridocyclitis which may be associated with arthritis as residues of the septicæmic stage. In addition there were arthritic pains at the onset suggesting rheumatism in 2 cases. Among 502 cases of cerebrospinal fever during the four years of the war there were 24 cases of arthritis, or 4·8 per cent.; 6, or 25 per cent., of the 24 cases were fatal. Orchitis or epididymitis without gonorrhœa occurred in 4 cases on the tenth, fifteenth, eighteenth, and eighteenth days of the disease. In 1 there was double orchitis, in the others (3 orchitis, 1 epididymitis) it was unilateral. In the fifth case there was pain in the epididymis without evidence of gonorrhœa for three days before the onset of meningococcic meningitis which terminated fatally four days later. This suggests the possibility that, like arthritis, orchitis and epididymitis may be the first parts of the body to suffer from local meningococcic infection. Among the 502 cases of cerebrospinal fever in the Navy during the four years of the war, orchitis or epididymitis without evidence of gonorrhœa was noted in 13 cases, or 2·6 per cent.

Relapses.—There is some uncertainty as to the distinction between the term relapse, which is best employed for a return of symptoms after the disease has apparently ceased, and recrudescence or return of the symptoms, as if from re-infection of the meninges, before the patient is really well. These recrudescences are extremely common; thus one patient who eventually died had seven. Genuine relapses are rare. Netter¹ appears to draw the line between recrudescences and relapses at a month, and found four examples of such relapses, or 1·6 per cent., among his 255 cases. One case among the 92 naval cases was discharged on leave and was subsequently reported to have had a relapse in a military hospital. A

¹ Netter, A.: *Bull. et mém Soc. méd. des hôp. de Par.*, 1918, 3e sér., xlii, p. 527.

man who had bacteriologically proved cerebrospinal fever in May, 1917, had another attack in February, 1918, at Deal, the cerebrospinal fluid containing meningococci which, however, were not agglutinated by any of Gordon's serums; after a normal temperature for twenty-three days he had a relapse, but eventually recovered. In another case the symptoms returned and the cerebrospinal fluid was found to be turbid sixteen days after the temperature became normal, though in the middle of the interval there was a febrile rise coincident with a serum rash.

Secondary or mixed infections of the cerebrospinal fluid occurred in 2 cases (both fatal); in one case, already mentioned in connection with acute otitis at the onset, there was a terminal pneumococcic infection. In the other there was a secondary streptococcic infection the day before death. Among the 339 cases in the Navy during the second, third, and fourth years of the war there were 8 cases of secondary or mixed infection of the meninges—4 with streptococci, 3 with pneumococci, and 1 with the tubercle bacillus; all but 1 (with pneumococci) proved fatal.

(3) SUMMARY OF THE RESULTS OF TREATMENT.

Four cases (all fatal) had lumbar puncture only, and 7 cases in addition to lumbar punctures had soamin (3 cases, 2 deaths), quinine (1 case, fatal), or soamin, quinine, and a stock vaccine (3 cases, all recovered). So that out of 11 cases not treated by serum 7, or 64 per cent., proved fatal. Out of 502 cases in the Navy during the four years of the war, 96 did not receive any serum, and of these 49, or 51 per cent., proved fatal; it is interesting to compare this mortality with that of 61 per cent. treated during the first year of the war with serum which was generally recognized as being inert. Among the 92 cases during 1917-18, 81 were treated by some brand of serum with a mortality of 27, or 29 per cent., as compared with a mortality of 95, or 32·7 per cent., among 295 cases treated during the last three years of the war; this, as pointed out before, forms a contrast to the mortality of 64, or 61 per cent., among 105 cases treated by serum during the first year of the war, when Flexner's serum was not available. During the second, third, and fourth years of the war 214 cases received Flexner's serum alone, or in combination with other serums, and 65 of these, or 30 per cent., proved fatal—the mortality of the 176 cases treated by Flexner's serum alone being 51, or 28·4 per cent., and of the 38 cases treated by Flexner's serum in combination with others, 14, or 36·8 per cent. During the fourth year of the war Flexner's serum was used in 71 out of the 81 cases treated by serum; and in 67 cases, with a mortality of 21, or 31 per cent., it was the only serum used. Of the remaining 10 cases treated by serums other than Flexner's, there were 3 deaths; these cases were given Lister's multivalent (6 cases, 1 death); Gordon's multivalent (1 case, fatal); Medical Research serum pooled and later type serum (1 case, recovery); Burroughs Wellcome and Co.'s serum (1 case,

recovery); and Lister's multivalent and Medical Research serum types 1 and 2 (1 case, fatal).

Out of the 81 cases 64, or 79 per cent., received the serum intrathecally within the first three days of the disease with a mortality of 21, or 32·8 per cent., which is lower than that of the 15 cases commencing serum treatment between the fourth and seventh days of the disease, namely, 40 per cent. Two cases in which the serum treatment was begun after the seventh day of the disease recovered. The results of the time allowed to elapse before serum treatment was begun in the 293 cases during the second, third, and fourth years of the war is shown below, but as 80 per cent. of the cases were injected with serum before the third day of the disease, the number of cases for comparison is small.

Day on which serum treatment began	Cases	Deaths	Recoveries
1st to 3rd day ...	234 ...	74 or 31·6 per cent. ...	160 or 68·4 per cent.
4th to 7th day ...	47 ...	18 „ 38·0 „ ...	29 „ 62·0 „
Later than 7th day ...	12 ...	3 „ 25·0 „ ...	9 „ 75·0 „
	293 ...	95 or 32·4 per cent. ...	198 or 67·6 per cent.

On the basis of an analysis of 1,211 cases Flexner showed that the mortality rose progressively with delay in commencing the serum treatment; but, on the other hand, the most severe cases are naturally those earliest sent to hospital, and the cases which survive for a week without serum treatment are probably those in which the symptoms are not grave, and so escape early diagnosis; they are certainly not fulminating, and probably some are so mild as to recover spontaneously—though from lack of proper treatment others will prove fatal later from hydrocephalus.

One case received intravenous, intrathecal, and subcutaneous injections of Flexner's serum on the second day of the disease, and rapidly improved. The only other case in which intravenous injection was employed proved fatal on the eighth day of the disease, and did not come into hospital until the sixth day. The intravenous injection of serum is, as insisted upon by Herrick, of value in the septicæmic pre-meningitic stage, and Flexner's contention that it is of little use against meningeal infection still holds good. Five cases (2 fatal) received serum hypodermically in addition to intrathecal injections.

The quantity of serum given intrathecally varied from 8 c.c. (in a fatal case) to 310 c.c. in a case that recovered. Another case after 455 c.c. intramuscularly and 85 c.c. intrathecally also recovered. The best results were obtained in cases receiving over 100 and less than 200 c.c. of serum. In addition to Flexner's serum intrathecally, 2 cases, when in a desperate condition, were given eusol; 1 case had 300 c.c. injected intravenously, and the other had it both intrathecally and intravenously; both proved fatal.

Anti-meningococcic vaccines were very rarely employed. As already mentioned, 3 cases (all recoveries) had a stock vaccine in addition to

quinine and soamin. Another case, after having 75 c.c. of Flexner's serum, passed into a chronic stage, and appeared to receive benefit from small doses of an autogenous vaccine, and, at any rate, made a complete recovery.

Serum Rashes, urticarial, erythematous, or morbilliform, occurred in 41, or 61·2 per cent., out of the 67 cases that received serum and survived for ten days, and on an average occurred on the tenth day after the first injection was given, the extremes being five and sixteen days; in one case there was a double serum rash on the fourteenth and forty-third days. In a man with an infected vaccination wound the serum rash appeared on the eleventh day after serum treatment was begun, and became hæmorrhagic the next day; as a boil appeared three days later the hæmorrhagic character of the serum rash may have been due to infection. In another case a purpuric serum rash was associated with sore throat. During the first four years of the war 308 cases have had serum and survived for ten days, and of these 140, or 45·5 per cent., have had a serum rash; the percentage of serum rashes has been much higher (50 per cent.) during the third and fourth years of the war, when 83 per cent. of the cases receiving serum had Flexner's serum, than in the second year of the war (30 per cent.) when only 41 per cent. of the serum-treated cases received Flexner's serum. The tendency of Flexner's serum to cause a serum rash was referred to in the report for the third year of the war. During the fourth year of the war out of 81 cases receiving serum 71 had Flexner's serum and 38, or 53·4 per cent. had rashes; but of these 71 cases 12 proved fatal before a serum rash could be excluded, so the incidence of serum rashes among 59 cases receiving Flexner's serum and surviving for ten days was really as high as 64 per cent. Among the 10 cases receiving various other brands of serum (Lister multivalent 6, Gordon's multivalent 1, Medical Research serum 1, Burroughs Wellcome and Co.'s serum 1, and 1 case both Lister's multivalent serum and Medical Research serum) 3, or 30 per cent., had a rash; but as 2 cases proved fatal before the serum rash could be excluded the incidence of the serum rash is really 3 out of 8, or 37·5 per cent.

The cases that received the smallest amounts of serum showed the lowest incidence of serum rashes, so far corresponding with the general opinion that the incidence of a rash is favoured by a large injection of serum. Among 59 cases that had Flexner's serum and recovered or survived for ten days, i.e., long enough to have had a serum rash, 6 received less than 50 c.c. of serum, and 2 (33·3 per cent.) had a rash; 11 received more than 50 c.c. and less than 100 c.c. of serum, and 7 (63·6 per cent.) had a rash; 24 received more than 100 c.c. and less than 150 c.c. of serum, and 18 (75 per cent.) had a rash; 7 received more than 150 c.c. and less than 200 c.c. of serum and 5 (71·4 per cent.) had a rash; 7 received more than 200 c.c. and less than 250 c.c. of serum, and 4 (57 per cent.) had a rash; 2 received more than 250 c.c. and less than 300 c.c. of serum and 2 (100 per

cent.) had a rash; 1 received more than 310 c.c. and had a rash; 1 received more than 455 c.c. intramuscularly and 85 c.c. intrathecally and did not have a rash.

Out of the 41 cases showing serum rashes 4, or 9·8 per cent., proved fatal. The duration of these 4 fatal cases was fourteen, nineteen, (pneumonia and empyema), thirty-six and ninety days respectively. Fourteen cases had an initial rash and a serum rash; 5 cases a serum rash and herpes, and 11 cases an initial rash, herpes, and a serum rash. In 2 cases there was œdema of the eyelids, which in 1 was accompanied by œdema of the face and extremities, at the same time as the serum rash. As the serum rash is often urticarial and as this is essentially a "serous hæmorrhage," it is surprising that œdema of the skin is not more often reported in association with a serum rash. In 3 cases arthritic pains occurred about the time of the serum rash; in 1 case which had panophthalmitis there was arthralgia two days before the rash was noticed; in another case the joints became painful the day after the rash appeared and four days before œdema of the eyelids was noticed; in the third case arthralgia lasting a week began two days after the serum rash appeared.

In 4 out of the 81 cases treated by serum there was a recrudescence of meningeal symptoms about the time of the serum rash; this serotoxic meningism, possibly due to changes in the meninges analogous to those in the skin, was discussed in the report for the third year of the war, and it was then pointed out that examination of the cerebrospinal fluid would decide, by showing the presence or absence of meningococci and the absence or presence of the normal reducing body of the cerebrospinal fluid, whether there was a true relapse or simply a manifestation of serum disease. If there is not a relapse, injection of serum does harm, thought to be the result of extreme hypersensitiveness to serum; out of the 4 cases, 2 received serum, 1 of which was made decidedly worse and subsequently proved fatal. Of the other two, 1 recovered.

Severe symptoms occurred in one case which received 15 c.c. of serum intrathecally on the thirty-fifth day of the disease, nineteen days after the last injection of serum; he died next day. These symptoms might well have been due to anaphylaxis, but eight days before his death he showed evidence—lethargy, vomiting, and incontinence—of increased intracranial pressure, and it is known that patients with distension of the cerebral ventricles due to obstruction of the foramina of Magendie and Luschka may react very violently to ordinary intrathecal injections of serum, the mechanism being thought to be congestion of the choroid plexuses and increased intraventricular pressure. Further, the patient was very seriously ill when the injection of serum was given.

As in the previous reports, I must express sincere gratitude to all the medical officers who have with never-failing courtesy and promptness assisted me in every way in obtaining notes and information about the cases.





