Type 28, a Group A streptococcus not belonging to any known type, and a Type 14 were implicated.

Type 28.—EI and FM had this streptococcus for a short while. FM was at the time severely infected with *Staph. aureus, Bact. coli, Strep. viridans,* and an organism resembling *Proteus melanovogenes* (Miles and Halnan, 1937), and the Type 28 had no observable effect.

In EI (and in FJ, see below) the appearance of the streptococcus sharply retarded the healing of an otherwise healthy wound containing only a little *Staph. aureus.*

Group A (U).—The untypable Group A infected FJ, and was responsible for the second of HT's hospital infections. There was no evidence of ill effect in HT. These two untypable A's are being investigated. If they prove to be serologically identical we might presume a cross-infection between HT and FJ, whose beds were only a few feet apart, for there were no other untypable A's in wounds or throats at the time.

Type 14.—SD first yielded Type 14 from a slowly healing wounded ear and from the throat. Subsequently, in the absence of any other demonstrable Type 14 in the ward, it appeared in HT, in FM as a *second* streptococcal infection, and in RM. SD was in the next bed to FM, and RM six feet away on the opposite side of the room. HT was the other side of the partition. Type 14 was not found again in SD's throat, but this patient was later infected by it, under the scab of a light wound that had healed over four weeks previously; the patient had been picking at the scab. FM's wound progressed very slowly, and required three operations in all. There is little doubt that the Type 14 infection was responsible for the delay and difficulties. RM's wound, initially infected with a few micrococci, healed slowly, but, considering the severity and situation of the wound and the presence of infected bone fragments, the delay could not unequivocally be attributed to the Type 14. Nevertheless the streptococcus constituted an unwelcome threat in an already serious situation.

But, whether the Type 14 proved to be deleterious or not, in the absence of any other demonstrable source of the organisms there can be little doubt that it spread through the ward and that the infection was carried from SD's throat or passed from wound to wound. Towards the end of the period the prevalence of Strep. 14 increased. At the routine swabbing on November 14 Strep. 14 appeared in three throats previously free from haemolytic streptococci. There were no signs of infection; three persons—two patients (including RM) and one nurse—thus became clinically undetectable reservoirs of Strep. 14.

(*d*) THEATRE INFECTION BY TYPABLE HAEMOLYTIC STREPTOCOCCI

In an E.M.S. theatre two patients, Mrs. A and Sergeant B, both clean cases, were operated upon on the same day, in the same theatre, and by the same team. The operations were the first and second on the morning of July 18, 1940, and were left cervical sympathectomy and repair of left brachial plexus respectively. Four days later Sergeant B's incision suppurated, and yielded a Type 11 streptococcus. A shallow ulcer eventually formed, which healed early in September. Five days after operation Mrs. A's incision broke down, and the pus contained Strep. 11. The patient became rapidly worse, and died a few days later from secondary haemorrhage from the subclavian artery. Throat swabs of all the theatre staff present on July 18 showed that one nurse was an abundant carrier of Strep. 11. It seems probable that she was the source of infection because, although there were other cases of Strep. 11 infection in the hospital at the same time, there was no discoverable association between these and the two patients, and no other source of infection was evident. The masks used in the operating theatre were too small to reach well under the chin, and consisted of two thicknesses of gauze with no interposed impervious material. The surgeon himself wore a large and impervious mask.

(*The second half of the paper will appear in next week's issue, together with the list of references.*)

CEREBROSPINAL MENINGITIS

THE USE OF SULPHONAMIDE DERIVATIVES IN PROPHYLAXIS

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The increased prevalence of cerebrospinal meningitis during wartime conditions has long been recognized, and the present war has proved no exception to the general rule.

The use of sulphonamide derivatives in treatment has brought about a marked decrease in the mortality rate, a shortening of the duration of the disease, and a great reduction in the incidence of sequelae. The application of these drugs to the prophylaxis of the disease has not, however, been so successful, and there is still no generally accepted routine procedure for the management of contacts. General measures, such as the swabbing and segregation of contacts, are usually employed, but have proved of doubtful value.

During the outbreak an opportunity was afforded of investigating a number of cases and of studying the effect of intensive sulphonamide therapy on the presence of the meningococcus in the nasopharyngeal mucosa. The results are given in two sections, the first dealing with the cases of cerebrospinal meningitis and the second with problems of prophylaxis.

Technique of the Investigation

Cerebrospinal Fluid.—Samples of cerebrospinal fluid were examined as soon after collection as possible. The deposit after centrifuging for five minutes was inoculated on to blood-agar and boiled-blood-agar plates and Loeffler's serum slopes; films were then made and 5 to 10 c.cm. of glucose broth was added to the remaining deposit. The cultures were incubated at 37° C. and examined daily for seven days. When growth was obtained subcultures were prepared on Loeffler's serum slopes; after twenty-four hours' incubation the subculture was suspended in normal saline, and macroscopic agglutination was carried out at 55° C. with Groups 1 and 2 sera. In a few instances the strains were kindly typed by Dr. W. M. Scott, Types 1 and 3 being identified. The films were stained by Gram's method and also by the technique recommended by Sandiford (1937) for urethral smears from cases of gonorrhoea.

Nasopharyngeal Swabs.—Material was collected from the nasopharynx by means of the West swab and cultured on blood agar. Boiled-blood-agar plates were also used originally, but as they invariably gave results similar to those from the blood-agar plates their use was discontinued. After incubation for twenty-four hours a close examination was made and suspicious colonies were subcultured on to Loeffler's serum slopes. If meningococci were not isolated the original plates were re-examined after incubation for a further twenty-four hours.

Only organisms agglutinating with one or other of the group sera were accepted as meningococci. The characteristic sugar reactions—that is, acid production in glucose and maltose but not in sucrose—were usually but not invariably given by the strains. While so-called inagglutinable strains have been reported by many workers it was considered that criteria other than serological tests were too unreliable for the differentiation of the meningococcus from other *Neisseria.* Wilson (1928), in an investigation of the *Neisseria,* found a considerable amount of

variability in Gram-negative cocci isolated from the nasopharynx, and considered that the classification of the organisms on the basis of colonial appearance was open to serious objections.

(A) Analysis of 51 Cases of Cerebrospinal Meningitis

Fifty-one cases of this condition have been investigated in various parts of the East and West Lancashire areas of the Western Command. These cases have all been sporadic, and it would appear that there is little justification for the general use of the term "epidemic" in connexion with this disease. Although in many instances conditions have been favourable for extensive local outbreaks, single cases have almost invariably been recorded. This is a usual feature of the disease, which is generally recognized as having a low morbidity rate, in contrast to such epidemic diseases as measles and influenza.

The *symptomatology* of the disease has been extremely variable. The commonest predominant features have been intense headache, neck rigidity, pyrexia, and vomiting. The onset, while usually sudden, has occasionally been slow and insidious. In a few cases in which vomiting has been pronounced the diagnosis has provisionally been one of acute appendicitis. The characteristic rash has been observed in several cases.

The *diagnosis* in all cases has been confirmed by an examination of the cerebrospinal fluid, which is purulent and often contains the causative organism. The meningococcus, however, may be neither seen nor cultivated, and occasionally when present in small numbers attempts at cultivation may be unsuccessful. This does not detract from the value of a lumbar puncture, which should be carried out in all suspected cases. Several patients have been seen with a clinical picture similar to that found in cerebrospinal meningitis, but the cerebrospinal fluid has been normal even on repeated examination; these cases have been kept under careful observation until a diagnosis has been established, and in no instance did meningitis develop. Cases of this kind in which a clinical diagnosis of cerebrospinal meningitis was not confirmed by lumbar puncture included such conditions as acute benign lymphocytic meningitis, sunstroke, frontal sinusitis, acute fibrositis of the neck, and even acute war neurosis.

The results obtained from the examination of fluids in the present series are given in Table I.

TABLE I.—*Isolation of Meningococci from the Cerebrospinal Fluid of Cases of Cerebrospinal Meningitis*

	No. of Cases	Group 1	Group 2	Not Tested
Meningococci isolated ..	23	21	0	2
,, not isolated ..	28	—	—	—
Total	51	21	0	2

Meningococci were isolated from only 23 out of 51 cases—i.e., 45%. In all instances, however, where serological tests were carried out (21 cases) the strains proved to be Group 1. This is in sharp contrast with the outbreak in 1915, in which Group 2 strains were commonly isolated. Organisms were not isolated in 55% of cases. These cases were undoubtedly cerebrospinal meningitis; in some a few organisms could be seen in films. The cerebrospinal fluid was usually collected within four days, often within two days, of the onset, but in the majority of cases intensive treatment with sulphanilamides or sulphapyridine had already been begun. This is probably an important factor in the failure to isolate meningococci, and emphasizes the need for early lumbar puncture, preferably before chemotherapy has been started.

Therapy in practically all cases was carried out on the lines recommended by Banks (1939) and the War Office Memorandum (1940)—that is, early massive doses of sulphanilamide or sulphapyridine, up to 10 grammes a day, for the first few days and the use of sulphapyridine soluble for fulminating cases or for cases in which the diagnosis had been delayed. The results have been highly satisfactory. The mortality rate has been low (less than 5%) and the incidence of sequelae slight.

(B) Problem of Prophylaxis

There is no generally accepted scheme for the control of cerebrospinal meningitis. It has been found that the meningococcus is well distributed in the general population and that the disease is spread almost entirely by carriers and not by actual cases of the disease. Control of the condition is therefore a difficult problem, and many methods have been advocated, the most widely employed being segregation and routine swabbing of contacts, with good ventilation and avoidance of overcrowding and fatigue, particularly in young recruits.

Value of Routine Swabbing

During the war of 1914–18 a considerable amount of research was carried out on various problems connected with cerebrospinal meningitis. Glover (1920) found that there was a definite relation between the incidence of the disease and the carrier rate of the population. An increase in the carrier rate over 20% was the warning signal for an outbreak of cerebrospinal meningitis. Glover (1918) also considered that overcrowding in sleeping quarters was a particularly important factor in the spread of the disease. Thus when the beds in barracks were placed more than two and a half feet apart there was a considerable reduction in the incidence of the disease. Emphasis was consequently laid on the swabbing of contacts and avoidance of overcrowding, particularly in barracks.

Dudley and Brennan (1934), however, were unable to correlate a high carrier rate in the population with an increased incidence of cerebrospinal meningitis. They found during an investigation at Chatham Naval Hospital a carrier rate of 13% with 11 cases of cerebrospinal meningitis; while later, over a period of some ten months, the carrier rate became 55% and yet no cases of meningitis developed.

Routine swabbing is now being viewed with disfavour as the results obtained hardly merit the labour involved. At the beginning of the war only "close-contacts" had to be swabbed—close-contacts being persons occupying adjacent beds or sharing the same billet or tent. This procedure has been carried out in all cases and 135 close-contacts have been examined. The results are given in Table II, together with those from a control group of patients in the hospital—usually cases of fracture, dyspepsia, or similar conditions—during the same period.

TABLE II.—*Incidence of Meningococci in Contacts and Non-contacts*

	No. Examined	No. Positive	Group 1 Strains	Group 2 Strains
Close-contacts	135	22 (16%)	6 (4%)	16 (12%)
Control group (non-contacts)	154	33 (21%)	5 (3%)	28 (18%)

There is little difference in the figures given by the two groups—the carrier rates being 16% for the close-contacts and 21% for the non-contacts. There was, however, a slightly increased proportion of Group 1 carriers in the close-contacts. In no instance did cerebrospinal meningitis develop in any of these individuals.

These results indicate that the swabbing of persons occupying beds adjacent to cases and the segregation of carriers do not serve any useful purpose as a routine procedure. Such a practice tends to give a feeling of false security, considering the wide distribution of the meningococcus in the community. Moreover, there is little justification for the assumption that only persons sleeping next to patients should be treated as close-contacts. It is highly probable that other persons, particularly those associated with cases during meal-times and recreational activities, might actually constitute closer contacts during the incubation period and early stages of the disease, when the organism is believed to be multiplying in the nasopharynx, and so be more liable to infection. Thus while a number of carriers are identified as a result of the swabbing of close-contacts, many others escape detection and continue to disseminate the organisms. Consequently unless swabbing is complete—and this is impracticable except in closed communities—it is without value.

Value of Sulphonamide Derivatives in Prophylaxis

The outstanding success obtained by sulphonamide drugs in the treatment of cerebrospinal meningitis has directed attention to their value in the treatment of carriers. Nothing of a definite nature has, however, been determined about this important question. Investigations were consequently carried out to obtain information about the presence of meningococci in nasopharyngeal swabs from: (1) persons under intensive treatment with sulphapyridine; (2) convalescent and recovered meningitis cases; (3) carriers after therapy with sulphapyridine.

1. *Persons under Intensive Treatment with Sulphapyridine.*—During the period March to September, 1940, a series of nasopharyngeal swabs were collected from patients in the hospital undergoing intensive chemotherapy for gonorrhoea. The swabs were usually obtained immediately after the first course of sulphapyridine (some 22 grammes): in a few cases as much as 60 to 80 grammes had been given before the swabs were taken. During the same period swabs have also been taken from other patients in the hospital who have not been receiving chemotherapy. The swabs have generally been collected in groups of four or five in order that each could receive adequate attention. The results are given in Table III along with those obtained from the close-contacts of cases of cerebrospinal meningitis (Table II above).

TABLE III.—*Isolation of the Meningococcus from the Nasopharynx of Individuals receiving and those not receiving Intensive Sulphonamide Treatment*

Cases	No. Examined	No. Positive	Group 1	Group 2
Treated with sulphapyridine ..	139	1	0	1
Close-contacts (not treated) ..	135	22	6	16
Control group (non-contacts)	154	33	5	28

There is a great contrast between the results given by patients receiving chemotherapy and those given by the other groups; in the former only one individual out of 139 gave a growth of a meningococcus; in the latter 55 out of 289 gave a positive result. It is interesting to note that pneumococci and *Strept. haemolyticus* were not infrequently isolated from the former group. It has been tentatively suggested, on evidence of a doubtful nature, that as there is a generic relationship between the meningococcus and the gonococcus some cross-immunity may exist between these organisms. Dudley and Brennan (1934), however, found a meningococcus carrier rate of 48% among 50 cases of gonorrhoea examined. The probability that the failure to isolate meningococci from treated gonorrhoea cases was due to the presence of some cross-immunity can therefore be excluded. It appears to be the direct result of the administration of the sulphapyridine.

2. *Convalescent and Recovered Meningitis Cases.*—A group of 14 recovered cases of cerebrospinal meningitis were examined at periods varying from 17 to 76 days from the onset of symptoms; in 9 cases the period was less than 40 days. In each case chemotherapy had been successfully applied. Meningococci were not isolated in any instance. This observation, while of little value in itself, provides some evidence to support the view that intensive treatment with drugs of the sulphonamide series is a satisfactory means of removing the meningococcus from the nasopharyngeal mucosa. It is generally accepted that the meningococcus produces a primary infection in the nasopharynx and that in some of these cases spread of the infection to the meninges takes place. Consequently in cases of cerebrospinal meningitis the causative organism can usually be isolated from nasopharyngeal swabs taken in the early stages of the disease. The meningococcus also tends to persist in this region during convalescence: Embleton and Steven (1919) found that every one of 86 cases of cerebrospinal meningitis investigated became a chronic carrier, with an average carrying period of six months. These figures form a sharp contrast to those given above.

3. *Carriers after Sulphapyridine Therapy.*—An attempt was next made to obtain more direct evidence of the value of sulphapyridine as a means of eliminating meningococci from the nasopharyngeal mucosa. Persons who had been found to harbour the meningococcus were segregated and given an intensive course of chemotherapy with sulphapyridine—4 grammes on the first and second days and 3 grammes on the third and fourth days. Nasopharyngeal swabs were collected before and after such treatment; the results are shown in Table IV.

TABLE IV.—*Treatment of Carriers of Meningococcus with Sulphapyridine*

	No. Examined	No. Positive	Group 1	Group 2
Before treatment	13	13	4	9
After ,, ...	13	0	0	0

While these figures, like those in the previous section dealing with recovered cases, are small, they provide further evidence to support the view that adequate treatment with sulphapyridine or allied drugs is a satisfactory method of clearing meningococci from the nasopharyngeal mucosa. In many instances the cultures prepared before chemotherapy gave an almost pure growth of the meningococcus.

Discussion

The epidemiology of cerebrospinal meningitis is a complex problem involving a close consideration of two main factors—namely, the virulence of the meningococcus and the resistance offered by the host.

The virulence of the meningococcus is difficult to assess as there is no laboratory animal in which virulence tests can be satisfactorily carried out. It is therefore necessary to depend on indirect evidence. Results obtained from the recent outbreak indicate unequivocally that Group 1 strains are at the present time more virulent than Group 2 meningococci. All identified strains from cases of cerebrospinal meningitis recorded here have been Group 1, and this appears to have been the usual finding in other parts of the country. As, however, Group 2 strains have produced meningitis in former outbreaks it cannot be assumed that

they are now permanently avirulent for man and are consequently of no epidemiological significance.

Fluctuations undoubtedly occur in the virulence and invasiveness of the meningococci. Maclean and Bevan (1939), investigating an extensive outbreak in Cyprus, obtained clinical evidence that suggested an increase in virulence of the meningococcus as a result of frequent passage from man to man. They recorded many instances of the rapid transfer of catarrh inside family circles, while only the last victims of the common infection developed meningitis. They did not, however, obtain any bacteriological confirmation of these observations.

It is consequently impossible to give any final opinion about the virulence of Group 1 and Group 2 meningococci, but there is no doubt that at the present time Group 2 strains are relatively avirulent and have a low invasive power. It is possible that changes may take place in meningococci analogous to those found in *H. pertussis*, where virulence progressively decreases from Phase I to Phase IV. It is interesting to note that while Group 1 strains isolated from cases of cerebrospinal meningitis usually gave clear-cut agglutination with little cross-reaction with Group 2 sera, strains isolated from carriers (mainly Group 2) frequently exhibited marked overlapping with the two group sera. Strains isolated from actual cases tended to show greater group specificity than strains isolated from carriers.

The spread of the meningococcus in the community is by droplet infection, and such factors as poor ventilation and overcrowding undoubtedly play an important part in the dissemination of the organism. They do not, however, appear to play a primary part in the development of the disease. Several of the 51 cases here recorded were associated with serious overcrowding; yet in no instance did a second case of cerebrospinal meningitis develop, in spite of the fact that such cases had often not been isolated for some twenty-four hours after the onset of the disease. A carrier rate of 21% was, moreover, found in the patients of the hospital; these were living under ideal conditions, with good ventilation and no overcrowding, the distance between adjacent beds being at least four feet. The organisms isolated, however, generally proved to be the relatively avirulent Group 2 strains.

During this investigation it has been repeatedly found that fatigue has been a contributing factor in the development of the disease. It is a common experience that the disease is found most commonly in young recruits and, under wartime conditions, vigorous training is started early, often in individuals unaccustomed to violent exercise. As a result resistance to infection is lowered rather than increased. The importance of overcrowding as a factor in the development of cerebrospinal meningitis appears to have been exaggerated, to the neglect of such factors as fatigue, which tend to lower resistance to infection.

The meningococcus is widely distributed in the community and, although the organism does not live naturally outside human tissues, its complete elimination is impossible. Swabbing is consequently of little value except in special circumstances, such as when a persistent source of infection is present in a closed community or during an extensive localized outbreak, where all contacts can be swabbed and carriers segregated and treated. These points have been stressed in the recent War Office Memorandum on Cerebrospinal Fever (1940).

The use of sulphonamide drugs in the treatment of carriers is likely to have only a limited application, as their wholesale administration is impossible. When, however, swabbing has been carried out and carriers have been identified these drugs should prove of great value, since other methods of treating carriers have proved unreliable. The results recorded here indicate that in adequate dosage the administration of sulphapyridine is an effective and rapid method of removing meningococci from the nasopharyngeal mucosa.

Summary

Fifty-one cases of cerebrospinal meningitis have been investigated; the meningococcus has been isolated on twenty-three occasions and, where typed, has been Group 1.

Evidence has been obtained that adequate dosage with sulphapyridine is a satisfactory method of clearing meningococci from the nasopharyngeal mucosa.

I wish to thank the many persons—in particular Mr. C. W. Ashton, senior laboratory assistant—who have assisted in various ways during this investigation.

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ANALYSIS OF HAEMORRHAGIC STATES WITH SNAKE VENOM AND LECITHIN

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In numerous experiments in man and animals we have confirmed the observations of Trevan and Macfarlane (1936–7) that the coagulant action of Russell-viper venom on blood and plasma can be potentiated by the addition of lecithin. Leathes and Mellanby (1939) and Pratt (1940), working with solutions of prothrombin, have shown that the venom acts as a thrombokinase, converting prothrombin into thrombin in the presence of calcium, and they have clearly demonstrated the adjuvant action of lecithin.

Method Used

All the observations in this paper were made by substituting venom or venom plus lecithin for the brain extract used in Quick's prothrombin test (Quick, 1935):

Nine cubic centimetres of blood, withdrawn rapidly and with special precaution to avoid trauma, are promptly and thoroughly mixed with 1 c.cm. of M/10 sodium oxalate, and centrifuged at a low speed for five minutes. Of this plasma 0.1 c.cm. is transferred to a dry clean test-tube (13 × 100 mm.) in a water bath kept at 37° C., and mixed with 0.1 c.cm. of venom or venom plus lecithin. Without delay 0.1 c.cm. of M/40 calcium chloride is added, the tube quickly shaken, and the exact time required for the formation of a solid clot recorded.

Under the conditions of Quick's test the optimum amount of lecithin is about 5 mg. per c.cm. of venom (Hobson and Witts, 1940), and the figure remains very constant under various experimental conditions, in different animal species, and in different members of the same species. This concentration is obtained by adding 0.05 c.cm. of a 10% alcoholic solution of ovolecithin to every cubic centimetre of the solution of venom. Different batches of Russell-viper venom as purchased vary in coagulant power, but phials from the same batch are very constant.