BACTERIOLOGICAL RESEARCHES ON CASES OF CEREBROSPINAL MENINGITIS, CONVALESCENTS AND CARRIERS.

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In this publication we desire to record the results of bacteriological experiments performed in the months of February, March, April and May, 1940, during an outbreak of cerebrospinal meningitis (c.s.m.) which affected the B.E.F. The opportunities provided allowed us to make certain comparisons between the existing conditions and the circumstances and general findings reported during 1915–19 by Mervyn Gordon, Tulloch, Glover and others in their classical observations on c.s.m. (see Special Report Series, Medical Research Council, No. 50).

As far as the epidemiological characteristics of the disease are concerned, it is likely that the predisposing factors which favoured the appearance of c.s.m. in the winter and early spring of 1939–40 were similar to those operating in 1918–19. Thus it is conceivable that the damp weather, the transference of large numbers of British troops to foreign soil, and the mass movement of civilians from vulnerable to safe areas of the country, resulted in a general interchange of nasopharyngeal bacterial flora which precipitated an outbreak of the disease. It is also likely that interference with the ventilation of public and domestic buildings enforced by the rigorous blackout conditions contributed towards the magnitude of the 1939–40 epidemic. Operating collectively, all these factors tended to increase the number of persons harbouring meningococci in the nasopharynx, so that pari passu the proportion of susceptible individuals liable to contract infection increased in number. For instance, the researches of Gordon (1919) demonstrated that, at the time of an epidemic among a mixed military population, the carrier rate was 20 per cent—a figure based on a very large number of examinations. Our own observations though limited in number also supported this view, for of 107 unselected contacts whom we examined from a wide area, 30 were positive, i.e. 28 per cent.

In the case of military camps and training establishments the carrier rate is higher (see Tulloch 1917); and Glover (1918) mentions that at a certain depot he found the carrier rate to be as much as 70 per cent during the period April-May-June, 1916. In short, as Gordon (1919–20) has expressed it, "the carrier rate is the pulse of the epidemic," and consequently, an outbreak of the disease is preceded by a rise in the carrier rate.
Whilst this may be so, it is equally true to say that a high carrier rate could exist without an epidemic, since the carrier rate is but a single factor—a feature well illustrated in the work of Dudley and Brenner (1934), who revealed that a carrier rate of 50 per cent could be maintained for over a year without c.s.m. developing. The indications are that whilst a high carrier rate may portend the occurrence of an epidemic under one set of circumstances, it may mean nothing among a community living amid different surroundings.

In theory it would seem that the most effective method of controlling c.s.m. would be to segregate and treat all carriers, but in actual practice this is obviously quite impossible owing to the very large numbers during an epidemic. Moreover, past experience has shown that, notwithstanding the diligence with which carriers are tracked down and measures employed to treat them, such action fails to stem the course of an epidemic. There is also the unpleasant prospect to be faced that a treated carrier is always exposed to reinfection. These views have been epitomized in the recently published Army Memorandum on Cerebrospinal Fever among Troops, February (1940) in the following three paragraphs where it is stated that: "wholesale swabbing of large numbers of persons serves no useful purpose . . .," that "carriers should be given such treatment as the officer in charge of the case and the pathologist may consider necessary . . .," and lastly that "segregation of individual carriers for a longer period than three weeks will seldom be necessary."

The data recorded in this paper were obtained when the old regulations were in force and at the time when wholesale swabbing was still in vogue, and many of our observations tend to reaffirm the finding of our forerunners in this field. Our investigations include a report on the good results following the treatment of c.s.m. carriers with sulphanilamide and c.s.m. cases with M & B 693, according to schema of dosages laid down in the latest Army Memorandum on Cerebrospinal Fever among Troops, dated October 23, 1940.

**TECHNIQUE OF ISOLATING MENINGOCOCCUS FROM NASOPHARYNGEAL SECRETION.**

Standard procedures were employed throughout. Briefly they were as follows. Having obtained a specimen of nasopharyngeal secretion with a West's post-nasal swab, a warm blood-agar plate was heavily inoculated by the multiple stroke inoculation method and incubated at 37° C. for thirty-six hours. At the end of this interval two or more suspicious colonies were picked off with a loop, subcultured on ordinary serum agar as well as ordinary agar media and incubated at 37° C. for twenty-four hours, at the end of which time films were made from each culture and examined for evidence of diplococci. In the event of growth developing on ordinary media the cultures were automatically discarded but, where growth appeared only on serum agar, further tests were performed by inoculating glucose and
maltose serum agar media. In the case of any typical meningococcal colonies which could not be subcultivated on ordinary agar and which fermented the sugars mentioned, final identification was achieved by testing the organism for agglutination with Group I and II anti-meningococcus sera.

**Effects of M & B 693 Treatment.**

*Clinical.*—200 consecutive cases of c.s.m. were treated with M & B 693 by Captain Morris, of which the last 83 were investigated bacteriologically by Major van Rooyen and the earlier 117 by his predecessor Lieutenant-Colonel F. J. Hallinan. The dosage employed varied according to the severity of the patient’s symptoms. A very ill man received 8 grammes daily for two days, followed by 6 grammes for three days and then 3 grammes daily for five days, the quantity of drug administered being 49 grammes over a period of ten days. A mild case was given 6 grammes daily for two days, followed by 4 grammes daily for two days and then 2 grammes daily for two days, altogether a total of 24 grammes in six days.

Only three deaths occurred out of 200 patients thus treated, no cases of agranulocytosis, severe haematuria or anuria were observed, and all the remaining patients recovered completely. We would like to add, however, that some complained of giddiness and fainting attacks during convalescence, in view of which complaints we would suggest that a minimum period for recuperation should be stipulated following an attack of c.s.m., for example, three months after a mild infection. Furthermore, we believe it would be a wise procedure to submit all recovered c.s.m. cases to specialist neurological examination prior to resumption of military service.

*Bacteriological.*—No organism could be demonstrated either in films or in culture in fifteen of the eighty-three cases investigated bacteriologically by C. E. van Rooyen. Sixty-eight stained films prepared from centrifuged cerebrospinal fluid (c.s.f.) revealed typical meningococci out of which sixty-two different strains of the organism were successfully cultivated, typed, and identified. These findings are in accordance with what is well recognized, namely, that meningococci are not always to be found, and occasionally may not be cultivable, although seen in direct films.

In view of the substitution of M & B 693 for antiserum treatment, we seized the opportunity of investigating day by day, in such cases as this was possible, the physical or other effects of chemotherapy on the cytology of c.s.f. in general and on the morphology of the meningococcus in particular. The results showed that, after the administration of M & B 693, the meningococcus rapidly disappeared from the c.s.f. It is scarcely possible to lay down any definite standards, but we have reason to believe that in the case of a heavy infection, in which a dose of 8 grammes of the drug is given on the first day, meningococci are no longer visible twenty-four hours later and thereafter the polymorphonuclear leucocytic infiltration subsides. The lymphocytes and monocytes are the last to disappear. With regard to the process by which the meningococcus is destroyed, it is obvious from a number
of films prepared from persons under treatment that about twelve hours after the drug has been given the organism begin to show swelling, haziness of outline and loss of diplococcal formation. This change is most marked in the extracellular cocci which are the first to disappear from the c.s.f., followed later by the intracellular ones and, on the second day of treatment, the majority of organisms represent partially disintegrated structures scarcely recognizable as meningococci. These observations suggest that M & B 693 exerts an inhibitory action on the growth of the meningococcus so that the extracellular forms die off and undergo involution as the result of bactericidal action, whilst the intracellular cocci become more vulnerable to phagocytic action. See also Colebrooke et al. (1936), McIntosh and Whitby (1939), Fleming (1940) and Oag (1939) for views regarding the mode of action of drugs of the sulphonamide class.

**Acute Meningitis without Meningococci in C.S.F.**

As mentioned earlier we encountered fifteen patients who showed all the classical signs and symptoms of meningitis without meningococci being visible either in films or culture. Thus no visible micro-organism could be blamed for the patient’s illness. There is little doubt, however, that the majority of these persons suffered from c.s.m., but we believe that among the fifteen, we encountered three patients whose clinical history and course of illness were typical enough to justify a diagnosis of benign Lymphocytic Choriomeningitis (l.c.m.) being made. This condition is also known by various other names, such as aseptic meningitis and Maladie d’Armstrong, and has been extensively studied in America by Armstrong and Lillie (1934), and in Great Britain by Findlay et al. (1936). A case occurred in the B.E.F. and was reported by Findlay, Stuart-Harris and MacCallum (1940). A full account of the disease, its diagnosis, and a comprehensive bibliography of the subject is to be found in the publication of van Rooyen and Rhodes (1940).

Unfortunately, in the three cases observed by us, it was not possible to confirm the diagnosis by isolating virus from the cerebrospinal fluid, or by tests to prove that specific antibodies existed in the patient’s blood but, nevertheless, it is correct to say that all cases were clinically and cytologically typical of acute lymphocytic choriomeningitis. The existence of l.c.m. emphasizes the necessity of keeping a sharp watch for its occurrence during epidemics of c.s.m., and, in consequence, special attention should be paid to cases of acute meningitis where micro-organisms are absent from the c.s.f. We would go so far as to propose that in every such instance, as a routine procedure, an effort should be made to recover l.c.m. virus from the c.s.f. and the patient’s blood should be examined for evidence of specific antibodies.

**Observations on C.S.M. Carriers.**

Thirty-six soldiers harbouring meningococci in the nasopharynx were treated by giving them orally 3 grammes of sulphanilamide daily for six
days. On the seventh and eighth day swabs were taken and examined for presence of the meningococcus by the usual methods. Thirty-five out of thirty-six carriers readily responded to such measures and became negative on the eighth day, but the remaining case, despite local treatment by the e.n.t. surgeon, continued to harbour the organism for several weeks and even resisted a second course of sulphanilamide. Two e.n.t. specialist examinations revealed no abnormalities. With obstinate cases such as this, it would be interesting to try the effect of larger doses of the drug, for instance, a total of 24 grammes given over a period of six days.

We believe that the general surroundings amid which these patients were nursed also contributed substantially towards the speed with which carriers became negative. Our cases were housed in well lighted and ventilated rooms of a hospital facing the sea and patients were encouraged to spend as much time as possible in the sunshine as part of their daily routine. Apart from the above, no other forms of treatment were prescribed and such remedies as nasal sprays, inhalations and gargles were not used. Obviously, owing to the small number of carriers thus treated, no definite conclusions can be drawn, but it is interesting to record that under the conditions described above, thirty-five out of thirty-six carriers yielded to treatment within eight days. We would also mention that several of the patients who were referred to us from other units were labelled as chronic carriers, and had failed to respond to treatment with antiseptics applied locally.

Observations on the Nasopharyngeal Bacterial Flora of C.S.M. Convalescents.

Carriers and Contacts—Before and After Chemotherapy.—With seriously ill patients it was not possible to secure post-nasal swabs without subjecting them to unnecessary discomfort and, consequently, we are unaware of what proportion of our c.s.m. cases also carried the meningococcus in the nasopharynx prior to treatment.

A rough estimate of the carrier rate was, however, obtained from the results of tests on 107 contacts serving in different areas in France, thirty of whom were found to be positive. Thus it is reasonable to infer that 28 per cent, or approximately a quarter of such contacts, were carriers and probably, in the case of actual c.s.m. patients, many more than this number harboured the meningococcus in the nasopharynx.

With reference to the 113 cases after treatment, these were swabbed twice prior to discharge from hospital and only three were found to be positive. It is conceivable that the latter cases may have been either resistant to M & B 693, or else have become reinfected in hospital. The results obtained with carriers following their treatment with sulphanilamide have already been mentioned.

General Conclusions.—Apart from the disappearance of the meningococcus from the nasopharynx of the majority of convalescents and carriers
after treatment, we also noticed that the drug appeared to diminish the incidence of other potentially pathogenic bacteria normally resident in the nasopharynx. For instance, during the winter months in France, although streptococcal sore throats were prevalent, in treated meningococcus cases and carriers it was found that streptococci were rarely cultivated and the bacterial flora in general seemed to be abnormally scanty in certain cases. Further investigations in this direction might provide valuable information regarding the effects of chemotherapy on the nasopharyngeal flora.

**Relative Incidence of Serological Groups.**

Sixty-two strains of meningococcus were isolated from different cases of c.s.m. and were identified as follows. After a preliminary direct slide agglutination test had been carried out, the result was confirmed by testing the organism for agglutination with six dilutions of standard Group I and II antisera varying from 1:30 to 1:960, the mixtures being observed in agglutination tubes. The control test consisted of an emulsion of organisms in which saline had been substituted for serum. For antigen an eighteen hours' old suspension of meningococcus in saline was usually employed without preliminary heating, but, in some tests as discovered by Gordon (1917), bacillary emulsion which had been heated to 65° C. for half-an-hour yielded better flocculation effects. All mixtures were incubated at 56° C. for four hours, after which a preliminary reading was made, followed by a second and final reading after the tubes had stood for twenty-four hours at room temperature.

The results demonstrated that, although according to the slide agglutination test 60 out of 62 strains were agglutinable by Group I and not by Group II serum and, presumably, all the strains were clearly divisible into two groups of meningococci, yet parallel quantitative macroscopical tests failed to yield identical results. According to the latter it was repeatedly noticed that the difference between the specific agglutinating properties of Groups I and II antisera was less sharply defined than the slide agglutination test had originally induced us to believe. For instance, sixty of the strains which were isolated were readily agglutinable by Group I serum up to an end-titre of 1:240 to 1:480, but, in each one of these tests, the same organism showed some degree of cross-agglutination with Group II antiserum in lower dilution, generally varying from 1:30 to 1:60.

**Group II Strains of Meningococci.**

*From C.S.M.—*Among various strains of meningococci which were recovered from spinal fluid (c.s.f.) strain "Damario" seemed to possess a double antigenic structure and was agglutinable with both Group I and II meningococcus antiserum, in each case up to 1:120 dilution of serum. However, after repeated tests it was eventually decided that the organism was more strongly agglutinated and in a higher titre by Group II than by
Group I antiserum and, accordingly, it was classified as belonging to Group II rather than Group I. A similar conclusion was also reached by Major Stuart-Harris, R.A.M.C., who very kindly provided a report on cultures sent to him. Dr. A. J. Rhodes of Edinburgh University likewise confirmed these observations. The subdivision of meningococcus strains into these two standard groups is thus not so sharp as may have been supposed, thereby supporting the earlier conclusions of Fildes and Baker (1918).

From Carriers.—Two other Group II meningococci were isolated from nasopharyngeal secretion and shown to be agglutinable up to a titre of 1:240 of serum and, like the others, cross-agglutination was also observed in a dilution of 1:30 with Group I antiserum.

The above results suggest the following conclusions: (a) Group I meningococcus was the predominant infecting organism responsible for the February-March-April outbreak in the B.E.F.; (b) certain strains of meningococcus (e.g. Damario) are of dual antigenic composition, being agglutinable to an approximately equal degree both by Group I and II sera; (c) meningococci classified as Group I contain varying amounts of the antigenic fraction characteristic of Group II; (d) this latter feature, however, is not detected by the slide agglutination technique.

It is of some interest that, of sixty-two cases of c.s.m. studied, sixty proved to be Group I infections; and of thirty strains isolated from the nasopharynx of carriers twenty-six were identified as Group I and four as Group II. On the face of it there seems to be no doubt that Group I meningococcus is the commoner organism, both in c.s.m. and in the carriers, but we have been unable to perform a larger number of examinations to warrant such deductions and our results are, therefore, only suggestive. It may well be that this was actually the case, and that the low incidence of c.s.m. due to Group II meningococcus was attributed to the small number of Group II meningococcus carriers. On the contrary it was equally conceivable that Group II meningococcus was more prevalent among carriers than our observations had led us to suppose and that its low incidence in c.s.m. was explicable on the grounds that the Group II meningococcus was less invasive and pathogenic than Group I meningococcus. This conclusion was reached by Griffith who also found that the majority of strains isolated from the pharynx were of Group II (see Muir and Ritchie 1937). Extensive investigation on c.s.m. carriers is still required before these outstanding problems can be solved.

Result of Blood Cultures.—Several unsuccessful attempts were made to recover the meningococcus from the blood in acute cases of c.s.m. prior to the administration of M & B 693. 10 c.c. of venous blood was obtained with strict aseptic precautions and inoculated into glucose broth medium, warmed to 37° C. prior to use and incubated at 37° C. for two days. Although the medium employed was capable of yielding luxuriant growths of meningococcus, our results proved negative throughout. Positive results were, however, obtained by Major H. C. Magnus and Major H. J.
Fidler of Nos. 2 and 3 General Hospital, B.E.F., from a case of chronic meningococcal septicæmia, an interesting condition which was studied originally by Soloman (1902) and lately by Dimson (1938). The strain of meningococcus supplied to me through the courtesy of Majors Magnus and Fidler proved to be a typical Group I organism. Colonel Hepple has informed me in a personal communication that Major Stuart-Harris also successfully isolated the organism from a case during the first week of the illness.

**MENINGOCOCCAL TONSILLITIS WITH PHARYNGITIS.**

We wish to report the occurrence of six cases of acute tonsillitis accompanied by pharyngitis due to meningococcus infection. The patients comprised a medical specialist, a surgical specialist, a chaplain and a private soldier, who had been repeatedly exposed to infection during the course of their duties, together with two other ranks from whom no definite history of contact with patients could be elicited. Clinically, the signs and symptoms complained of by these individuals were very similar; the onset was sudden, the throat was painful, the tonsils were acutely inflamed, general malaise was present and in two cases a transient pyrexia reached 100° F. and lasted for two days. In general, the appearance of the throat and fauces was not unlike that observed in early acute streptococcal tonsillitis. All six cases readily responded to treatment with M & B 693, and were discharged to duty in ten days.

**Bacteriological Findings.**—From four patients a profuse growth of typical Group I meningococcus was isolated and in the remaining two a mixed growth of meningococcus and *Streptococcus viridans* was obtained. Scattered colonies of *Staphylococcus albus* and *aureus* were also present but no significance was attached to their occurrence. Apart from the bacterial flora mentioned, other common pathogenic organisms usually found in this site could not be demonstrated, and thus a search for haemolytic streptococci, *B. diphtheriae*, Vincent's organisms, and *Monilia albicans* proved to be negative. Also in the last two cases a possible herpes virus infection was excluded by scarifying the cornea of a guinea pig and examining this histologically for evidence of inclusions. From the above investigation it was concluded that four of the cases we studied were acute tonsillitis caused by the meningococcus alone, and the remainder were due to the meningococcus associated with *Str. viridans*.

**AGGLUTINATION TESTS WITH CONVALESCENT PATIENTS' SERUM.**

In the past, since the majority of c.s.m. cases received antimeningococcal serum on admission to hospital, investigations into the occurrence of specific agglutinins in patients' blood were not of much significance. However, with the advent of chemotherapy, it is now possible to investigate this aspect of the disease, and consequently we tested the blood of twenty-six convalescent cases of c.s.m., varying from the seventh to the forty-ninth day after the
onset of illness, for evidence of agglutinins. The technique of the test was identical with that described earlier for grouping of the meningococcus and, on this occasion, dilutions of patients' serum ranging from 1:30 to 1:960 were used and, in addition to the saline antigen control, an extra antigen check was incorporated which consisted of normal human serum plus antigen.

Results Obtained with Normal Serum (taken from healthy soldiers during the months of March, April and June).—Eighty-four control sera (which were negative to the Kahn reaction) were examined. In no instance were agglutinins for the meningococcus found to be present in a serum dilution of 1:30. In a limited number of experiments a series of lower serum dilutions varying from 1:4 to 1:64 was set up, and here likewise the results were negative throughout. These results suggest that natural agglutinins for the meningococcus are absent from normal human serum even in low dilution.

Results with Sera of C.S.M. Cases and Convalescents.—The earliest sign of an agglutination reaction was observed in one case on the seventh day after the onset of patient's illness and the patient's own Group I meningococcus, as well as another strain isolated from a different patient, were agglutinated by the serum to an end-titre of 1:30. No cross-agglutinin for Group II meningococcus could be found and, in a few cases, by means of agglutinin-absorption tests, it was possible to demonstrate that all Group I agglutinins could be completely removed from a patient's serum by first treating it with either the homologous infecting strain or with another Group I meningococcus. The latest time after c.s.m. at which agglutinins could be demonstrated in patients' blood was the forty-ninth day when a 1:30 dilution gave a positive result. Tests with sera obtained after this time were invariably negative. The period at which the highest agglutination response was recorded was approximately about the twenty-first day after the onset of the disease, at which stage of convalescence the serum frequently reacted in a dilution varying from 1:120 to 1:240. From the twenty-first to the forty-ninth day considerable variation in results was noticed and, in general, it seemed that the increase of agglutinins was a transient phenomenon which quickly appeared and disappeared. In some cases no agglutinins could be demonstrated at any stage throughout the illness, even though the patient's own strain of organism was used as antigen, and for this we could offer no explanation except to suggest that the rapidity with which M & B 693 acted allowed no time for their development.

Discussion.

Owing to circumstances, our researches were terminated before we were able to perform as many tests as we would have liked to have done. The results, nevertheless, indicate that, after a case of c.s.m. has been cured with large doses of M & B 693, it is uncommon to find such individuals harbouring meningococci in the nasopharynx.
Regarding carriers, our experience with a few, thirty contacts, suggests that a short course of M & B 693 consisting of 3 grammes daily for six days, is enough to make the majority negative, and we would recommend that carriers who prove resistant should be given a full course consisting of 6 grammes daily for two days, 4 grammes daily for two days, and 2 grammes daily for two days, the total quantity administered being 24 grammes over six days.

The cases of meningococcal tonsillitis and pharyngitis reported are of particular interest as they illustrate the necessity for examining all throat swabs, especially during the time of a c.s.m. outbreak, not only for the common pathogenic organisms such as streptococci and B. diphtheriae but also for the meningococcus. This organism should be regarded as a definite cause of sore throats, and we deprecated the tendency to call all gram-negative nasopharyngeal diplococci "M. catarrhalis" so often without cultural and serological confirmation. We would advocate that, in future epidemics, watch should be kept for meningococcal tonsillitis and these cases be treated promptly. There is much to support the view of some bacteriologists, e.g. Professor Mackie (personal communication), that the condition of c.s.m. is primarily one of epidemic rhino-pharyngitis and secondarily one of meningitis.

The work of Kennedy (1926), followed by the more recent observations of Stott and Copeman (1940) on chronic meningococcal septicæmia, has drawn attention to yet another aspect of meningococcal infection and it was in this connection that a search for specific agglutinins in cerebrospinal meningitis cases was undertaken. It was not always possible to diagnose chronic meningococcal septicæmia, popularly referred to among members of the B.E.F. as Stott's disease, with certainty, for it was seldom that a positive blood culture could be obtained and often nasopharyngeal throat swabs remained negative throughout the patient's illness. Thus the recognition of the disease usually depended on clinical evidence alone, coupled with the dramatic effect of M & B 693 treatment, the patient becoming afebrile within twenty-four hours. In all suspected cases of Stott's disease agglutination tests should be done employing Group I and II suspensions of meningococcus, as antigen, and from our experiences in cases of c.s.m. we would be inclined to interpret as positive agglutination produced by patient's serum diluted 1:30 or upwards.

According to the researches of Bell (1920), specific complement-fixing antibodies to the meningococcus are also developed in the sera of c.s.m. cases after the fourth day of illness, and these tests should also be utilized. The greatest obstacle to the application of serological reactions in the diagnosis of meningococcal infections is the fact that although at present two antigenic groups of the organism are recognized and designated Group I and II respectively, much still remains to be learnt regarding the precise antigenic composition of the meningococcus. In view of the work of Stott and Copeman (1940) on chronic meningococcal septicæmia this aspect
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of the problem acquires a fresh significance and, in cases of meningococcal septicæmia, the patients' serum should be tested for agglutinins, not only against Group I and II meningococcus but also against standard suspensions of Gordon's (1920 a) four types of meningococcus.

In conclusion, we would make the statement that in its clinical, bacteriological and epidemiological aspects the meningococcus is an organism the pathogenesis of which is still imperfectly understood and, although our observations are incomplete, we hope that some of the issues we have raised will merit consideration in future epidemics.

CONCLUSIONS.

(1) Out of 200 cases of cerebrospinal meningitis treated with M & B 693, only three died (mortality 1·5 per cent). In eighty-three consecutive cases the use of M & B 693 not only cured the disease but also abolished the carrier state during convalescence. The average age of our patients was between 20 and 30 years old.

(2) Encouraging results were obtained in a small series of thirty-six carriers, thirty-five of whom became negative following treatment with 18 grammes of sulphanilamide administered over a period of six days.

(3) Six cases of acute meningococcal tonsillitis are reported, and the importance of this condition is emphasized in relation to the carrier problem.

(4) Observations on the occurrence of specific anti-meningococcal agglutinins in patients' sera have confirmed the earlier researches of Gates (1918) and Bell (1920). Such agglutination reactions are often feeble in character and liable to escape attention unless care is exercised whilst performing tests.

(5) The advent of chemotherapy has enabled us to reinvestigate the subjects of serum agglutinins free from the artificial effects caused by the introduction of therapeutic anti-serum. It has been shown that antibodies which are present from the seventh day of illness attain their maximum on the twenty-first day and thereafter swiftly decline.

(6) The possible value of agglutination tests as an aid to the diagnosis of chronic meningococcal septicæmia is discussed.

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