If when this piece of bone is very gently removed haemorrhage from lacuna or sinus occurs, one is in a position to see the bleeding point clearly and to control it. The sinus should not be plugged with gauze. The haemorrhage can be arrested by applying a piece of tissue cut from the under surface of the flap, as Sir Victor Horsley originally suggested; if this is pressed gently down upon the bleeding point for a few minutes it will adhere firmly to the dura and control the bleeding effectually, but without obliterating the lacuna or sinus, as is almost certain to occur if gauze plugging is employed. This method has been found satisfactory. It encourages re-establishment of the cortical venous drainage, and leads to a diminution of such intracranial pressure as was due to oedema. Should the compression, however, persist, it may be advisable later to perform a decompressive operation, but of the effect of such a secondary operation we are not yet in a position to express an opinion.

It must not be supposed that we are recommending extensive operations in all cases, or even in a large proportion. Naturally, the indications in each individual case must be considered carefully, and the question as to what symptoms an operation may relieve or prevent must be answered before the exact nature of the contemplated operation can be determined. Indiscriminate extensive operations might well prove as discouraging in their results as indiscriminate limited trephining.

We desire to emphasize this point, as it is, of course, possible to do much harm in one case by an operation which would be wholly suitable in another.

The drawings have been kindly made by Dr. W. Crampton Gore, British Red Cross Society.

EPIDEMIC CEREBRO-SPINAL FEVER:

THE PLACE OF THE MENINGOCOCCUS IN ITS ETIOLOGY.

A BACTERIOLOGICAL STUDY.

(Preliminary Note.)

BY

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Is the Meningococcus the Primary Infective Agent?

It is believed by many authorities that the meningococcus of Weichselbaum is the primary infective agent in the disease known as epidemic cerebro-spinal fever. And it is also believed, both in the profession and outside it, that the available evidence in support of this view is satisfactory.

Briefly the evidence is based on the following facts:

1. The frequency with which the organism can be isolated from the naso-pharynx, cerebro-spinal fluid and blood in acute cases of the disease, and from the meninges and other tissues *post mortem*.
2. Its frequent isolation from the naso-pharynx of primary and secondary contact carriers.
3. In some ascertained carriers the disease subsequently develops with typical meningococci in the cerebro-spinal fluid or elsewhere.
4. Its presence in the naso-pharynx of carriers acting as a theoretical bridge from one epidemic to the next.
5. Meningitis can be produced in monkeys after exposure of the arachnoid and injection of living cultures of the organism, or by direct inoculation into the spinal canal.
6. The injection of antisera produced by injection of cultures of the meningococcus is sometimes followed by cure.
7. Emulsions of the organism can often be agglutinated by the serum of a patient suffering from the disease.

Taken together these seven points constitute at first sight a formidable mass of proof.

Before discussing their true value it may be well briefly to enumerate the few ascertained facts which suggest that the meningococcus, as we know it in artificial culture, may not be the cause of the disease, however much it may prove to be responsible for the more or less terminal event of meningitis.

These facts are:

1. The attendants on acute cases of the disease rarely contract it, although the percentage of such acute cases harbouring the organisms in the first few days is very high.
2. For every case of the disease there are ten to fifty carriers, but of detained carriers of the meningococcus in the naso-pharynx only few develop cerebro-spinal fever.
3. Injection of cultures of the meningococcus into monkeys elsewhere than into the meninges or spinal canal does not reproduce the disease, or meningitis.
4. Agglutination reactions with serum from cerebro-spinal cases are often unsatisfactory both at 37° C. and at 55° C., both with autogenous and with heterogenous emulsions.
5. The marked instability of the organism in the laboratory, both culturally and biochemically.

These five points, whilst not disproving the reputed etiological relationship of the meningococcus to the disease, at the same time suggest that extreme care is needed in judging of the value of the positive evidence usually relied on.

A good deal of stress has been laid on the fact that cure may follow the injection into the spinal canal of Flexner or other antiserum. Against this must be set the fact that in the present epidemic Flexner's results have not been reproduced. Moreover, not a few cases, even of extreme gravity, recover without specific treatment, and we have no control observations to show the value of the injection of normal serum; and, thirdly, as suggested by Dr. W. M. Fletcher, it is conceivable that careful control observations may show that simple puncture alone may be as beneficial as injection of normal serum, or of antiserum.

The evidence afforded by antisera is, therefore, at present worth little. The evidence derived from the occurrence of a fatal meningitis in monkeys after the formidable procedure of exposing the arachnoid, followed by injection of cultures of the meningococcus, is of small value, since meningitis can be produced in monkeys by other organisms when injected in the same way, and we have no evidence that meningeal infection can produce cerebro-spinal fever, however capable it may be of setting up meningitis.

The evidence afforded by agglutinability of the organism by serum from cases of the disease must not be taken too seriously, because we now know that secondary invaders are capable of specific agglutination even in relatively high titre. And in the absence of experimental evidence to the contrary we cannot at present deny that the meningococcus may be only a secondary invader, as was suggested at a recent discussion on the subject, just as a streptococcus may be in scarlet fever.

Moreover, apart from secondary invasion, the mere presence of the meningococcus, however frequent, in acute cases of the disease, or in healthy carriers, does no more than suggest a causal relationship. In the absence of good collateral evidence, and especially of experimental reproduction of the disease in animals, the association does not prove that the meningococcus is the cause of epidemic cerebro-spinal fever. And finally, we have yet to show that the meningococcus occurs frequently in the blood in abortive cases with fever in a disease that frequently presents all the clinical features of a septicaemia. On the whole, therefore, it would appear to be unwise to make dogmatic statements that the meningococcus, as we know it, is the cause of epidemic cerebro-spinal fever, though this does not imply that the future may not provide better evidence than at present exists. The purport, in short, of this note is to show that the evidence at present available, however suggestive, is inadequate, and to plead the necessity for fresh research into the etiology of the disease.

In illustration of the possibilities opened up by fresh research on this subject, the following results of a bacteriological study of the urine in the disease may be related. The observations are at present incomplete, and are only brought forward now in the hope that other observers of the disease will enter the same field and will record their results before the present epidemic has run its course.

As I have shown elsewhere, working with Dr. Ingram, the bacteriological study of the urine in all cases of continued fever, however slight, deserves greater attention from clinicians and experimentalists than it at present receives, both in diseases in which the causal organism is known as well as in those in which it is not.

When, therefore, the present epidemic arose, I sought for, and readily obtained, facilities from the War Office for examination of specimens of urine, as well as of blood and cerebro-spinal fluid and swabs from the throat, in acute cases.

For this purpose I invited the collaboration of my laboratory colleagues at Addington Park War Fever Hospital—Dr. C. E. Lakin, Dr. T. H. C. Benians, and Dr. Elizabeth H. Lepper—who have shared with me the labours of this inquiry.

Is the Meningococcus merely a Phase of the Causal Organism?

The starting point of our work was the thesis that in cerebro-spinal fever the meningococcus might prove to be a late non-infective phase in the life-history of a minute organism not yet discovered, which is only infective in its earlier stages—that is to say, it is only in these early stages that it causes the disease. If this be so, the early infective phase might prove to differ widely, morphologically, culturally, and biochemically, from a late non-infective meningococcal phase. The basis for this theory was the fact that Hort and Ingram had already described a minute pleomorphic organism in typhus fever, and had produced experimental evidence, not yet completed, which suggested that this minute organism was in its earliest phases the primary infective agent in that disease, whilst the late phases were non-infective. They had, in fact, shown that typhus urine, blood, and cerebro-spinal fluid often contained a minute pleomorphic organism which appeared rapidly to develop into larger organisms morphologically indistinguishable, apart from size, from one of the minute forms, and that the large form was non-infective to monkeys, whilst the minute forms produced in these animals a disease characterized by fever at the end of a latent period, the minute forms and large forms being again recoverable from the injected monkeys. Now these large forms had been noted by numerous observers, some of whom claimed that they were the primary infective agents. This they certainly are not, and they must therefore either be contaminations or secondary invaders, or must represent late stages of some undescribed organism. That they were contaminations is an unnecessary aspersion on the numerous competent observers who have recovered them from the blood in various parts of the world, and the large percentage of cases in which they have been recovered in some epidemics makes the theory of secondary invasion no more probable than in the case of the meningococcus in cerebro-spinal fever, especially as they were found by Hort and Ingram to be preceded by the minute pleomorphic form in many cases, the latter always rapidly disappearing. Hence, without making undue claims, it may reasonably be said that in cerebro-spinal fever, as in typhus, there is a clear case for investigation.

In connexion with the question of minute organisms, without or within the limit of vision, which subsequently develop into larger forms, arises the interesting problem of how organisms reach the meninges and cerebro-spinal fluid from the blood stream. It is true that the majority of organisms capable of producing meningitis do not do so even when present in the blood in large numbers, except in rare instances. In some of these, as in tubercle, an obvious explanation can be found. In the case of cerebro-spinal meningitis it is possible that at some phase in the life-history of the organism the latter exists in so minute a form in the blood as to be able to pass through the filter bed between the circulatory and cerebro-spinal systems. And, as will be seen with our experiments

with filtered urine, and as Hort and Ingram showed with filtered typhus urine, this may prove to be a good explanation.

Experimental Evidence.

We have in cerebro-spinal fever—thanks to the courtesy of the commanding officers, bacteriologists, and medical superintendents at Caterham, Aldershot, Stockwell, and Wandsworth—examined the urine of 19 acute cases, the blood of 15 cases, the cerebro-spinal fluid of 4 cases, and throat swabs from 3 cases. In the great majority of these we have found, isolated, and as far as possible identified, especially from catheter specimens of urine, the Gram-positive and Gram-negative organisms of Jaeger, at one time believed to be identical with the meningococcus of Weichselbaum. The organism of Jaeger appears to be identical with the *Diplococcus crassus*, and possibly with the organisms described respectively by Heubner, by Lepierre and by Lehmann. It was claimed in 1903 by Allbrecht and Ghon that Jaeger's meningococcus is quite distinct from the meningococcus of Weichselbaum, but this question will have to be re-examined. Jaeger's organism was in his cases (mainly isolated from the throat, but in our cases we recovered it frequently from the fresh urine, and from incubated urine (catheter specimens), from incubated citrated blood kept in sealed flasks. The organism in question on artificial culture (serum-agar, ascitic-agar, nasagar), and in incubated natural media, is a somewhat larger organism than the meningococcus of Weichselbaum, and it occurs as a rounded diplococcus, in pairs and tetrads, and sometimes in short chains. It resists heating at 58° C. for an hour, and emulsions in saline resisted the action of toluol for thirty minutes. In early cultures (twelve to twenty-four hours) Gram-negative forms are sometimes as numerous in a field as are the Gram-positive individuals. On subculture Gram-positive organisms appear to predominate. The reaction of these organisms on the sugars approaches that of the staphylococci. They do not coagulate milk or produce indol in peptone water. In some cases the organism produced acid readily in glucose, but slowly in lactose and saccharose, and was without action on mannite or inulin. In two cases glucose alone was fermented, maltose unfortunately not being at the time available. The organisms emulsify freely in saline, and the two strains tested were not agglutinated by antimeningococcal serum, but gave equivocal results with serum from cases of the disease in man.

When once established on media containing ascitic fluid or serum, they grow readily on agar or in broth. Confluent transparent minute colonies, at first greyish, becoming opaque in a few days, give on film preparations a thin bluish smear, which is sometimes difficult to see. Even in young cultures the Gram-negative individuals sometimes take up the counter-stain with difficulty; in others the counter-stain is well taken up. The transparent colonies soon become opaque on culture plates. These organisms occurred so frequently in catheter specimens of urine in sealed flasks as to constitute a useful indirect aid to diagnosis, which was frequently confirmed by the clinical history and by the isolation of Weichselbaum's meningococcus from the cerebro-spinal fluid. It is not here suggested that the "meningococcus" of Jaeger as found in some specimens of urine, blood, and cerebro-spinal fluid is the same organism as the meningococcus of Weichselbaum, from which it presents well-marked cultural and biochemical differences. Its frequent presence, however, in our cases suggests that further study of its relationship to the latter, in the urine and blood especially, is much to be desired.

In addition to this organism, we also frequently found, in films of fresh urine, cerebro-spinal fluid, and blood (in order of frequency), Gram-negative and Gram-positive bacilli, both very small and large. Cultivation of this organism from the cerebro-spinal fluid and from most of the specimens of blood unfortunately failed. In two cases, however, a small Gram-negative bacillus was isolated from the incubated citrated blood, and in a few cases from the urine. Gram-negative bacilli in the cerebro-spinal fluid in cases of cerebro-spinal fever have been often described by Arkwright and other observers. Some workers have referred to them as members of the haemophilic group,

such as Pfeiffer's bacillus. The strains we isolated from the urine grew readily in broth without the addition of serum or blood, and did not give coliform reactions.

In several of the urines, both in fresh catheter specimens and in incubated samples, considerable numbers of Gram-negative diplococci were seen, often in clumps. They also occurred free in pairs and in tetrads. They mostly had flattened opposing surfaces, and were morphologically indistinguishable from meningococci or gonococci. In some of the films they varied from 0.1 to 0.4 μ in their greatest diameter. They were sometimes to be found in epithelial cells from the bladder, and sometimes in clusters. In no case were any considerable number of pus cells seen. The diplococci could not be cultivated as persistent Gram-negative organisms, but appeared to merge into Jaeger's organism, colonies of Gram-positive and Gram-negative rounded individuals alone surviving.

In all the specimens of urine examined in the fresh state, turbidity of varying degree was present. This turbidity was in no case due to pus cells, to blood, or to crystalline phosphates, as gauged by microscopical examination of centrifuged deposits. It was determined, therefore, to filter a specimen of fresh turbid urine from an undoubted case with meningeal symptoms through a tested Berkefeld filter. Filtration was completed in five minutes, and a few loopfuls of the filtrate were spread over the surface of a nasagar plate, proved to be sterile by previous incubation. Examined after four days the plate showed a minute growth. A single colony under a low power lens was grey, punctate, and showed a broken outline. Films were made from this single colony and showed:

- (a) Large numbers of Gram-negative diplococci, morphologically indistinguishable from the meningococcus, also a few Gram-positive forms, the former staining feebly with methylene blue.
- (b) Small Gram-negative bacilli.
- (c) Gram-positive and Gram-negative organisms morphologically similar to Jaeger's meningococcus.
- (d) Gram-negative rod-shaped organisms, with two to six Gram-negative "granules" in its long axis at regular intervals, occasional Gram-positive "granules" being sometimes seen. Each granule was composed of a diplococcus, with flattened opposed surfaces. In some the terminal diplococcus was detached, and was indistinguishable from the meningococcus of Weichselbaum.
- (e) Gram-positive diplo-bacilli, which were sometimes unequal in size.

From the unused portion of the single colony an emulsion was made *in situ* (that is, on the original plate) with a loopful of broth, and fresh plates of nasagar were inoculated in series. These were examined after forty-eight hours, and extremely minute colonies were found in clusters. These under the low power lens were again seen to be grey, punctate, and to have irregular outlines. Films made from these colonies, which were too small to be picked off individually for smears, again showed the films (a) (b) (c) (d) (e) as in the first single colony, with the exception that Jaeger's rounded meningococcus appeared to predominate, Gram-positive organisms being numerous. These small colonies were again subcultured on to fresh nasagar plates, and the growth examined in twelve hours. The colonies now present were, many of them, extremely small, but were all similar in appearance to each other under a low power as regards colour, outline, and punctuation. They were also transparent to the naked eye, and film preparations from isolated colonies, slightly larger than those on the first subculture plate, showed (c) (d) and (e) only, the diplococcal flattened organisms resembling the meningococcus of Weichselbaum being no longer found. Gram-positive organisms, both bacilli and rounded diplococcal forms similar to Jaeger's organism, predominated. The biochemical and serological reactions of this strain of this apparently pleomorphic organism are now being studied, and fresh filtrates of new specimens of urine sown.

It is, of course, obvious that in single colonies showing organisms of diverse morphology and staining reaction pleomorphism is easier to suggest than to prove. In all such cases mixtures of different organisms may be present

which are not derived from a common ancestor, and severe tests of pleomorphism must be established. So far the organisms referred to have successfully passed these tests, though much further work is required before any definite statement can be made as to this or as to the relationship of the various organisms here noted to the meningococcus of Weichselbaum. Enough, however, has been said to justify a plea for extensive bacteriological examination of the urine, side by side with that of the blood, cerebro-spinal fluid, and naso-pharynx, in the present declining epidemic of cerebro-spinal fever.

Disinfection of the Urine.

Owing to the fact that a highly pleomorphic organism appears to be present, bacteriological study of the urine in this disease is one of great complexity and difficulty; but it is, perhaps, not unreasonable to suggest that the meningococcus is only a phase in the life-history of the true infective agent in cerebro-spinal fever is one that is worth full investigation. And in the meanwhile it would appear to be wise to disinfect the urine of all known cases, and of all known carriers of Weichselbaum's meningococcus.

It will, of course, be understood that the presence in the urine of the meningococcus, or of organisms related to it, in no way removes the necessity for examination of the throats of contacts and of secondary carriers as at present carried out, since whatever the true cause of the disease, the meningococcus is certainly associated with it. And even if the meningococcus be eventually shown to be a harmless phase in the life-history of the true infective agent discharged into the urine, it will still be wise to disinfect the latter, as advised by other workers who consider the case for the meningococcus to have been fully proved.

CEREBRO-SPINAL FEVER: DIAGNOSIS AND TREATMENT.

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IN connexion with Colonel Hobhouse's valuable contribution¹ regarding the diagnosis of cerebro-spinal fever, I wish to contribute a few notes on the disease from our experience at the 1st Eastern General Hospital at Cambridge.

In my own open-air ward I have had 19 cases, and have seen two cases at another centre in the command and four other cases at the Eastern General Hospital under Major Wright, which I have included in this paper. This gives a total of 25 cases, which have been drawn from a very wide area, comprising places in Cambridgeshire, Huntingdonshire, Norfolk, Essex, Bedfordshire, Hertfordshire, Buckinghamshire, and Northamptonshire. Three stations supplied ten cases between them. In fourteen instances the patients appear to afford solitary examples of the occurrence of the disease in the locality. Of these 25 cases, 5 have died—a mortality of 20 per cent.—and 2 have been already discharged cured. In 19 the meningococcus was recovered from the cerebro-spinal fluid. In the other 6 the diagnosis was indisputable from the history and clinical symptoms.

In this connexion I should like to refer to certain difficulties in the bacteriological diagnosis which Captain Gaskell has kindly pointed out to me. In several of the cases the cerebro-spinal fluid has proved sterile at the first puncture, but the organism has been grown at a subsequent one. The organism—a Gram-negative diplococcus growing within the cells—is rarely found in smears taken direct from the cerebro-spinal fluid, but has to be cultivated. When, however, the organism with its characteristic intracellular growth is easily found in smears in the cerebro-spinal fluid, either in the first instance or at the second or third attempt, its presence is of grave prognostic import. A further point is the presence or absence of sugar in the cerebro-spinal fluid; this, which is generally absent in the first instance, may reappear as the case improves, and again disappear in a relapse.