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NOTES ON THE SERUM THERAPY
OF
MENINGOCOCCAL MENINGITIS

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"The Association could of course not authoritatively sanction the tapping, but under certain circumstances it might be tried."

So spake the President of the South African Medical Association in 1898 in reply to a medical practitioner who in the course of a discussion on cerebrospinal meningitis asked whether, in view of the fatal nature of the disease, he might not be justified, if he got a good case, in tapping the spinal cord.

This reads strangely in these days when lumbar puncture for purposes of diagnosis and treatment is a routine procedure in cases of meningitis. But even more recently, in 1906, Osler, writing about the treatment of this disease, referred to lumbar puncture in a none too hopeful way as something which seemed helpful in a case with coma or convulsions and which, in any case, did no harm. The lines of treatment then in vogue against meningitis were wet-cupping in the nape of the neck, cold to the head and spine, hydrotherapy in the form of a tub-bath at body temperature given every three hours and counter-irritation with the thermo-cautery at the back of the neck. Internally, quinine in large doses, ergot, belladonna, calabar-bean, potassium iodide and other drugs were in favour as measures against the infection.

Osler emphasised the serious nature of the disease and drew attention to the high case-mortality rate. He indicated that intraspinal injections had been tried and mentioned that in one of his cases Cushing opened and drained the spinal canal. The nature of the substance injected are not recorded but curiously enough he noted that diptheria (?) antitoxin had been used with success in an epidemic of meningitis in New York.

At about this time, however, the foundations of the future treatment of meningococcal meningitis by means of serum were being laid down in the experimental work of Simon Flexner and his colleagues in the laboratories of the Rockefeller Institute. In 1907 these men inoculated animals with the meningococcus in suitable doses and obtained antimeningococcal serum which was found to be of value in the treatment of experimentally induced meningitis in the monkey. This heralded the dawn of a new era in the treatment of the dread disease. At first the serum was obtained from the smaller laboratory animals and then from the goat and horse. Soon the serum was applied to the cure of human cases of meningitis and the results were so encouraging that the immunization of horses was undertaken on a large scale and antimeningococcal serum was prepared in bulk.

Flexner studied the statistics of case mortality in meningococcal meningitis during the period 1904—1909 when the disease was very prevalent in a wide area of the United States and Canada and indeed was epidemic in other parts of the world as well. In a number of American cities the case mortality rate varied between 70 and 90 per cent. and in Great Britain 70 and 80 per cent. In Germany in 3085 cases of the disease the rate was 42 to 67 per cent. In France and Belgium the figures were 75 and 78 per cent. respectively. Thus in the pre-serum days the fatality rate was in general about 70 per cent.

The new antimeningococcus serum prepared at the laboratories of the Rockefeller Institute was widely distributed for clinical trial with the object of obtaining from as an extensive an area as possible an evaluation of its worth in the treatment of cases of meningitis under different conditions and circumstances. The results of these experiences derived from cases in America, Asia, Europe
and Australia were finally collected and analysed. A clear and definite indication of the value of the serum emerged from this enquiry. Thus in 1294 cases of meningococcal meningitis there were 400 deaths, a case mortality of 30.9 per cent. As compared with the pre-serum days the case mortality was thus reduced to less than half. At the same time the advisability of giving the serum as early on in the course of the disease as possible was made clear. The following figures are of striking interest in this connection.

<table>
<thead>
<tr>
<th>Day of disease when serum was injected</th>
<th>Case mortality per cent.</th>
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<tbody>
<tr>
<td>1st—3rd</td>
<td>18.1</td>
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<tr>
<td>4th—7th</td>
<td>27.6</td>
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<tr>
<td>Later than 7th</td>
<td>80.5</td>
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Other interesting figures to show the value of the serum were taken out by Flexner. Thus, in Texas in 1911 and 1912 in 1956 cases of meningococcal meningitis 562 received no serum and 1394 were given the benefit of one or more injections of the serum. In the latter the case mortality was 37 per cent. while in the untreated cases the figure was as high as 77 per cent.

As a result of these world-wide clinical trials Flexner could say in 1913 “... the antitoxin meningococcus serum when used by the subdural method of injection in suitable doses and at proper intervals is capable of reducing the period of the illness; of preventing and large measure the chronic lesions and types of infection; of bringing complete restoration of health in all but a very small number of the recovered thus lessening the serious, deforming and permanent consequences of meningitis and of greatly diminishing the fatalities due to the disease.”

In subsequent years, confirmation of the beneficial effects of meningococcal serum therapy has come from many quarters, the most recent, perhaps, being by Wadsworth who showed that the case mortality in 606 cases of cerebrospinal meningitis properly treated with the six-strain New York serum was only 17.8 per cent. over the period 1920 to 1930.

In South Africa, too, the changed outlook on the almost inevitably fatal nature of the disease became evident with the introduction of serum therapy. When the original Rockefeller serum was distributed for trial small quantities were made available in the Transvaal. In 1915 Turner and Brebner on the Witwatersrand were so impressed with the value of the serum that they considered it would almost amount to criminal neglect if health authorities in any centre did not have a supply of serum available where cerebrospinal meningitis was liable to occur. They treated 60 cases of the disease with the American serum, there were 25 deaths, a case mortality of 41 per cent. This of course compares very favourably with the case mortality of 70.25 per cent. recorded by Turner in 279 cases of cerebrospinal meningitis among mine natives of the Witwatersrand goldfields in the earlier days before the employment of serum therapy. The more so indeed because the overseas serum could not have been entirely effective against any but the strains of the meningococcus common to both America and South Africa, leaving cases of the disease caused by locally important strains of the organism practically untreated from the immunological point of view. The importance of preparing a local antitoxin meningococcal serum was soon recognised and the preliminary work of identifying the various strains of the meningococcus isolated from current cases of cerebrospinal meningitis was carried out by Lister in 1919. He found that the majority of strains of the organism belonged to Group I (Gordon) but that other strains not infrequently occurred. This investigation culminated in the preparation of a local serum antigenically covering the strains of the organism responsible for infection.

The results of the use of the South African serum were very gratifying. Rapidly the knowledge of this valuable new weapon against the disease spread and medical men in increasing numbers adopted serum therapy in their cerebrospinal meningitis cases. No systematic study has as yet been published in this country with regard to the case mortality in the disease with the use of serum, but opinions expressed by medical men are entirely favourable to its therapeutic employment.

The Preparation and Standardisation of Antimeningococcal Serum.

Horses, after a careful examination as to their physical condition and freedom from disease, are inoculated intravenously with suspensions of live meningococci and autolysates of these organisms belonging to the different strains over a period of two or three months.

Constant control is kept of the reactions in horses during the course of the immunization, and, indeed, the dosage of the antigen injected is regulated by any such reactions
that may occur. The blood serum of the animals is tested at various intervals during the immunization period and when an agglutinating titre of 1:10,000 is shown the horse is bled to the amount of about 10 litres. The blood is collected in sterile vessels and allowed to clot, and the separated serum to which is added 0.3 per cent. of tricresol as a preservative is kept in the refrigerator at a temperature just above freezing point until required. It is then filtered through Seitz filters and distributed into double-ended ampoules holding 25 c.c. each. Sterility tests are carried out on each batch of serum so prepared.

In the preparation of antituberculous serum it is necessary that the final product be polyvalent against the different strains of the responsible organisms. For this purpose the antigen used in the horse immunization process consists of representatives of the various mycobacteria isolated locally from the cerebrospinal fluid in cases of meningococcal meningitis.

The preparation of a universally effective serum is, however, attended with considerable difficulty owing mainly to the antigenic multiplicity of the meningococcal types. Unlike the pneumococcus, for example, the strain differentiation of the meningococcus is not clear-cut; group specificity is not definite, as antigenic factors common to two or more groups may be found. Hence the laboratory procedure of testing the value of the serum by its agglutinating action on the organism is not satisfactory. In any case the agglutinating titre of the serum is not necessarily a true reflection of its therapeutic value. In practice, however, this test, inadequate though it be, is largely employed in default of a more efficient method. In purely exotoxic diseases like diptheria the protective value of the serum against fatal doses of the toxin in laboratory animals is a good guide to its protective value in man. The meningococcus, however, has but a slight action on laboratory animals and in any event the action is irregular and thus the protection test for the standardization of antituberculous serum is of little value.

The Therapeutic Use of Antituberculous Serum in Cerebrospinal Meningitis.

As soon as possible after the disease has been diagnosed the patient should be given the benefit of serum therapy. Early and adequate treatment is all important.

A lumbar puncture is performed under aseptic conditions in the 3rd or 4th lumbar space. The cerebrospinal fluid should be allowed to flow out until the pressure is so reduced that only three to four drops come out per minute. The serum previously warmed to body temperature is then injected in a quantity slightly less than the amount of fluid withdrawn. It is advisable to raise the foot of the patient's bed in order to assist in the distribution of the serum in the spinal canal. A general anaesthetic is not usually necessary. The serum should now be administered intrathecally by the gravity method, that is to say under a low pressure easily controlled by the mere raising or lowering of the height of the serum container above the patient. The use of a syringe for the injection should be avoided on account of the danger of injecting the serum forcibly producing an unduly high pressure in the cerebrospinal system.

For the gravity method of injection the following procedure may be followed. Warm a 25 c.c. ampoule of antituberculous serum to body temperature by immersion in water at 40°C (104°F) care being taken not to overheat. While this is being done sterilize the following, (a) a piece of rubber tubing 1/2 to 1 inch in diameter and from 2 to 3 feet long. It is advantageous to have a window in the tube in the shape of a piece of glass tubing about one inch long and let in about two inches above one end of the tubing, (b) a clip which is to be used to compress the tube when necessary and so stop the flow of serum, (c) a lumbar puncture needle fitted with stylet. Perform the lumbar puncture withdrawing the requisite amount of cerebrospinal fluid. Leave the needle in situ. With a small file make a mark completely around the longer tube of the ampoule close to the bulbous part and break off. To the end of the ampoule now attach the rubber tubing which is clipped at the lower end. In the same way as before open the other tube of the ampoule. Release the clip and slowly allow serum to run down until all the air is expelled and the rubber tube is full of serum. Reapply the clip and attach the free end of the tubing to the lumbar puncture needle. Release the clip and proceed to administer the serum holding the ampoule 12—18 inches above the level of the needle.

Throughout the period of the injection the pulse and respiration should be carefully watched and these must guide the rate of inflow of the serum.

In the actual treatment of a case of cerebrospinal meningitis a dose of 25 c.c. of serum is given intrathecally. This dose should be repeated every 12 hours in severe cases and
every 24 hours in mild cases until a definite improvement is shown. Larger doses are occasionally desirable, the volume being influenced by the amount of cerebrospinal fluid withdrawn. Some authorities advocate the giving of intravenous injections of the serum in addition to those administered intraspinally. This may in some cases be an added strength in the battle against the disease to guard against the effects of the meningococcal septicemia which is frequently associated with the meningitis. There is evidence that in cerebrospinal meningitis owing to the action of the meningococcus on the nerve centres the arterial tension is not constantly at its normal height throughout the disease. In the circumstances it is a wise precaution to give the intravenous injections very slowly to prevent the shock that might follow the too rapid introduction of the serum into the blood circulation. In order to permit of a gradual and continuous absorption of meningococcal antibodies into the system 25 c.c. of the serum may be injected intramuscularly at the same time as the intrathecal dose is given.

Sometimes blocking of the spinal canal occurs and as a result the serum does not reach the meninges of the brain nor of the full length of the cord. In such a case the lumbar puncture must be performed at a higher level and indeed it may be necessary to carry out a cisternal puncture with the injection of the serum into the cisterna magna. By this method the danger of a cord block hindering efficient drainage of purulent fluid and of preventing the full action of the serum is removed. The technique of cisterna puncture is not difficult but as the injection is made through the atlanto-occipital ligament in the neighbourhood of the medulla it is obvious that great care must be exercised. It is recommended that the operator practise this technique first on the cadaver before attempting cisterna puncture in a patient.

The method of cisterna puncture advocated by Ayer is as follows:—"The patient is placed on his side as if for lumbar puncture with the neck moderately flexed. Care is taken to maintain the alignment of the vertebral column to prevent scoliosis and torsion. After antiseptic preparations of the skin usually including the shaving of a little hair (and local anaesthetisation with novocain if this is considered necessary) the thumb of the left hand is placed on the spine of the axis and the needle inserted in the middle line just above the thumb. The needle may be pushed rapidly through the skin but should then be cautiously and guardedly forced upward and forward in line with the external auditory meatus and glabella until the dura is pierced. If the cisterna be entered at this angle there is usually a distance of from 2.5—3.0 c.c. between dura and medulla as shown by frozen sections; with the needle less oblique in position the distance between the walls of the cisterna become progressively less. Therefore it is good practice to aim a little higher than the auditory meatus and if the needle strikes the occiput to depress just enough to pass the dura at its uppermost attachment to the foramen magnum. At its entrance the same 'give' is felt as in lumbar puncture.'"

Goldman and Bower at the Los Angeles General Hospital treated fifty cases of cerebrospinal meningitis with specific serum by the cisterna route and forty eight cases by ordinary lumbar puncture. In both methods the intravenous injection of serum was used in addition. The advantages lay entirely with the cisterna puncture method. Generally a smaller amount of serum was required involving a lesser number of cord punctures. The case mortality was 52.5 per cent. by the lumbar puncture method and 25.5 per cent. by the cisterna puncture method. Further, an average of 25 per cent. longer time was spent in hospital by the patients in the lumbar puncture group. The authors state that over 700 cisterna punctures have been done by them. No untoward results were observed and they unreservedly recommend the method.

The therapeutic efficiency of serum medication in meningococcal meningitis can obviously only be fairly adjudged if due regard be had to the technique of injection and the adequacy of dosage.

Bibliography.