Original Articles.

THE METHOD OF ADMINISTERING ANTI-MENINGITIS SERUM.

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THE value of serum therapy in epidemic cerebrospinal meningitis has been a subject for discussion for more than a year; in fact, ever since the antiserum prepared by Flexner at the Rockefeller Institute for Medical Research has been in use. While almost all of those who had experience with the serum were soon impressed with its evident marked effect upon the symptoms and course of the disease, positive conclusions could not be drawn from a comparatively small number of cases. Even when continuously favorable reports were being received from a number of observers in widely separated localities, Dr. Flexner was unwilling to admit that the value of the serum treatment could be considered proved and waited until he should receive reports from a greater number of cases. Now, however, these reports have been received, and convincing proof of the value of this treatment has been offered by Flexner and Jobling in a recent publication,¹ which contains an analysis of 400 cases of epidemic meningitis treated with the antimeningitis serum. The conclusions of the authors are as follows: "It is our belief that the analyses of histories of cases of epidemic meningitis which have been presented in this article furnish convincing proof that the antimeningitis serum, when used by the subdural method of injection, in suitable doses and at proper intervals, is capable of reducing the period of illness; of preventing, in large measure, the chronic lesions and types of the infection; of bringing about complete restoration to 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."

Acting upon a suggestion recently made to me by Dr. Flexner, it is my purpose in this paper to call attention to the words "when used by the subdural method of injection, in suitable doses and at proper intervals" contained in these conclusions. It has been convincingly shown that the results to be expected from the use of the serum are, to a considerable extent, dependent upon the period in the course of the disease when serum treatment is begun, and upon the initial severity of the case. My own experience with the use of the serum in 57 cases of epidemic meningitis has lead me to believe that the results are also largely dependent upon the method of administering the treatment.

NECESSITY OF USING SUBDURAL INJECTION ONLY.

The technic of the actual injection of the serum has been sufficiently described in the various publications of the last year.² Yet there

may still be some who do not fully realize the necessity of giving the serum by subdural injection, and who might be tempted to waste valuable time, or even to nullify its effect, by attempting to use it by the method of subcutaneous injection employed with diphtheria antitoxin. The efficacy of the serum depends directly upon its concentration. The reason of its efficacy is found in the site of the disease. In epidemic cerebrospinal meningitis, the site of the disease is bathed in the cerebrospinal fluid, which fact fortunately permits us by subdural injection to apply the serum in a concentrated form exactly where it is needed. If the serum is injected subcutaneously, it is so diluted by absorption into the general circulation that all the good effect of concentration is lost. Moreover, it does not pass readily from the blood into the cerebrospinal fluid. As a consequence of these facts, no good result may be expected from the subcutaneous method of injection.

In the earlier days of my experience with the serum I used the subcutaneous method in a small number of cases. These were cases in which no cerebrospinal fluid could be withdrawn by lumbar puncture, and at that time I did not dare to give a subdural injection of the serum without the previous withdrawal of cerebrospinal fluid for fear of bad results from the increase of intradural pressure. For this reason subcutaneous injections were tried, and in none of these cases were there any of those effects which so strikingly follow the subdural injection of the serum. Later, when the good results of subdural injections became more and more manifest, it appeared to me that the risk of danger from increased intradural pressure was well worth taking and I have frequently injected the serum into the spinal canal in cases where no fluid was obtained. In but one case has any noticeable disturbance followed this practice, the case of a very young baby, in which the injection of the serum was followed by a temporary collapse, with cyanosis, irregular respiration and weak pulse, but in which complete recovery occurred. The number of cases in which no cerebrospinal fluid can be obtained is so very small that this question does not often arise and consequently positive conclusions cannot yet be drawn. My present belief is that the danger to be apprehended from increased intradural pressure in these cases is small in comparison with the danger to be apprehended from not giving the serum by subdural injection, and consequently that the method of subdural injection should be used in all cases.

I have touched upon this side of the subject only because I have recently been often addressed with questions as to the possibility of using subcutaneous injections of the serum. My principal purpose is to discuss the doses, the intervals between doses and the indications for and frequency of their repetition.

When the serum first came into use it was in an experimental stage. Its users had no positive information on these points. We only knew

¹ Jour. of Exp. Med., vol. x, No. 5, September, 1908.

² BOSTON MED. AND SURG. JOUR., vol. clviii, No. 12, pp. 370-379, March 19, 1908.

that a maximum dose of 30 ccm. had been used, and that sufficient cerebrospinal fluid should first be removed to make room for the serum injected. A good deal of the earlier use of the serum was experimental, and we tried various doses and various intervals of repetition. Gradually these experiments have led to the formation of a conception of a proper method, the best method of using the serum.

THE SIZE OF THE DOSE.

First, as to the size of the dose. In the earlier days of the use of the serum the rule was to inject a quantity of serum no greater than that of the cerebrospinal fluid withdrawn up to a maximum of 30 ccm. It soon began to appear that those cases in which only small amounts of cerebrospinal fluid could be obtained by lumbar puncture, and in which only small doses of 10, 15 or 20 ccm. were given, did not do so well as the cases in which full doses of 30 ccm. could be given. So marked did the difference appear that I became convinced that the benefits to be derived from larger doses were great enough to counterbalance the possible risk of increasing the intradural pressure and I began to use larger doses, even in cases where only very small amounts of cerebrospinal fluid could be obtained. Up to the present time this practice has resulted in no disturbance, except in the one case referred to above. I then raised the maximum dose, in cases in which plenty of cerebrospinal fluid could be obtained, to 45 ccm. without bad effects. Doses of 30 ccm., in most cases, appeared to give sufficiently good results, but doses of less than 30 ccm. appeared almost constantly to give less good results.

My present belief is that the larger the dose the better is the result, and that as large a dose as possible should be given in all cases. The limit is still the risk of disturbance from increased intradural pressure, and just how great is that risk, time alone can determine. I believe that 30 ccm. should be a minimum rather than a maximum dose, and that in most cases this quantity can and should be given. The exceptions are found in very young babies, and in a few other cases in which only a small amount of cerebrospinal fluid can be obtained, and in which, on attempting the injection of a full dose, after a certain point further injection appears to encounter an abnormal resistance. This last point of resistance can only be judged fully by practice. After giving a sufficient number of subdural injections, one becomes accustomed to a normal standard of the feeling of resistance and is sensible of any increase above the normal.

In all cases it is absolutely essential to withdraw as much cerebrospinal fluid as can possibly be obtained before injecting the serum. There are two reasons for this: first, so that as large a dose as possibly may be given with the greatest safety, and second, because it is probable that the creation of negative pressure in the upper parts of the cerebrospinal system favors the diffusion of the serum to the remoter parts affected by the disease. It is now believed that the failure

of the serum in certain so-called resistant cases is due to a sufficient quantity of the serum not reaching remoter parts, such as the cerebral ventricles, and that the wide diffusion of the serum can be favored by the creation of a comparative degree of negative pressure in these places. It is possible that this diffusion can also be favored by placing the patient with the head low immediately after the injection is given.

After the withdrawal of the cerebrospinal fluid, if the quantity withdrawn is 30 ccm. or under, the routine dose should be 30 ccm. except in case of the exceptions mentioned above. The aim should always be to give 30 ccm. if possible, and a smaller quantity should not be given unless a distinct feeling of resistance is encountered. If the quantity withdrawn is more than 30 ccm., the quantity of serum injected should be equal to the quantity of cerebrospinal fluid withdrawn. In very severe or fulminant cases, especially in adults, in which the quantity of fluid withdrawn is between 30 ccm. and 45 ccm., I believe that 45 ccm. should be given, provided that no sensation of abnormal resistance is encountered.

FREQUENCY OF REPEATING THE DOSE.

A second point in the method of using anti-meningitis serum which is under discussion is when and how often should the injections be repeated. Here again the earlier work with the serum was more or less experimental. The majority of cases in which the serum was used early in the course of the disease showed a distinct and often very marked reaction after one dose, this reaction consisting in a rapid fall of temperature and a marked improvement in all the symptoms, particularly in the mental condition, which at times changes within twelve hours from one of unconsciousness to one of complete consciousness. In some of the cases in my series this improvement after one dose was permanent and progressive, and recovery was uninterrupted without further doses being given. In other cases the improvement after one dose was not complete and the condition remained stationary or tended after a time to get worse again. It seemed then that the best method of using the serum would be to repeat the dose at those times when the limit of improvement from from any one dose should have appeared to have been reached, that is, when the condition was stationary or beginning to get worse. I treated a number of cases in this way and it soon appeared that those cases in which there was little immediate improvement, or which early showed a tendency to remain stationary or relapse, in which in consequence frequently repeated doses were given at the outset, did better than those cases in which the initial improvement was more marked and in which in consequence repetitions of the dose were postponed and later strung along at intervals. This method of repeating the dose when the effect is exhausted, of striking at the disease, as it were, each time it attempts

to raise its head, is a plausible and attractive method, but I am now convinced that it is not a good one.

I am now convinced that it is better to repeat the injections a number of times at the outset in all cases, and that by so doing the improvement is more likely to be permanent, the course of the disease is more likely to be short, and that the liability to relapse is greatly lessened. As to just how often the dose should be repeated at the outset, the last word cannot yet be said, and for the present the number of repetitions must, to a certain extent, be arbitrary. The best guide is found in the disappearance of the diplococci from the cerebrospinal fluid, although this disappearance is no proof that diplococci have disappeared from all parts of the cerebrospinal tract.

As a routine, I believe that in all cases the injections should be repeated daily so long as diplococci are found in the cerebrospinal fluid, no matter how many doses must be given. The finding of diplococci in cover-slips is a more reliable test than the results of culture, as the ability of the diplococcus intracellularis to grow in cultures is very variable and very easily influenced by the serum, one dose often being sufficient to produce a sterile culture, even when diplococci can be found in the fluid withdrawn at the next lumbar puncture. In cases in which diplococci disappear early from the cerebrospinal fluid, the injections should be repeated daily for four doses. This number four is an arbitrary one, but is based on the experience of a number of observers and, although undoubtedly in some cases fewer might suffice, yet, as one can never know beforehand, I believe four to be the safest number to be used in this class of cases to insure obtaining the most permanent improvement and the greatest freedom from relapse.

I believe also that in certain fulminant or very severe cases the injections should be repeated oftener than once in twenty-four hours. This belief is based on two fulminant cases in my series which ended fatally. In both the first injection was followed by a distinct period of improvement occurring within twelve hours, and in one this improvement amounted to a return to consciousness. In both cases, when I returned in twenty-four hours to give the second injection, the patients were already moribund, having become rapidly worse during the few hours preceding my arrival. On the other hand, in another fulminant case, the second injection was given during the period of greatest improvement, ten hours after the first, and in this case improvement was maintained and complete recovery occurred. I think it very possible that the two fatal cases might have been saved if the injection of the serum had been repeated sooner. The very fact that the effects of the serum appear so soon after its injection is an argument for its more frequent repetition, as a more rapid reaction is more apt to become sooner exhausted in so severe a disease. Therefore, I believe that

very severe or fulminant cases should be very closely watched and that the physician should stand by ready to give a second injection the moment the period of initial improvement shows any tendency to cease, and that if they cannot be so watched, or if there is no period of improvement, the injection should be repeated in twelve hours instead of twenty-four.

MANAGEMENT OF PROLONGED CASES.

In some cases, even when the initial treatment has been carried out as outlined above, recovery does not immediately occur. In a few, organisms may continue to be found in cover-slips. In such cases the only treatment is to continue to give daily doses indefinitely until either the diplococci disappear or the disease ends fatally. I have only known one such case. So long as diplococci can be found in the cerebrospinal fluid there is hope for a good result from repeated injections of the serum. The majority of prolonged cases are cases in which treatment has been begun comparatively late in the course of the disease, and in which diplococci disappear, but in which symptoms are not entirely relieved. When such cases are progressing steadily, even though slowly toward recovery, nothing further need be done. When, however, the condition of such patients shows a tendency to remain stationary, with certain symptoms still persisting, or to become worse, then further treatment is indicated. In this connection the persistence of retraction of the head, rigidity of the neck and Kernig's sign is not of great importance, as these symptoms tend to persist longer than others without influencing the final outcome. In some of the most favorable cases they persist long after all other symptoms have disappeared, and their persistence is not an indication for further treatment. When, however, any subjective symptoms, such as pain, or any fever or any abnormality of the mental condition persist, then further treatment is indicated. After the initial course of treatment has been given, one may wait about four days, unless the persisting symptoms are serious, when one should wait only two or three days. Then the injections should be repeated. If diplococci have reappeared in the cerebrospinal fluid, then full doses should be repeated daily until the diplococci have again disappeared. If diplococci have not reappeared, four full doses should be injected on successive days, when one may again wait a few days and then again repeat four full doses, and this routine should be continued as long as the patient's condition is stationary or becoming worse, with fever, subjective symptoms or a mental condition other than full normal consciousness, or until the chronic stage of the disease is fully established.

MANAGEMENT OF CHRONIC CASES.

In the chronic stage the consciousness remains affected, but the temperature is normal and the patient's condition remains indefinitely stationary, with no diplococci in the cerebrospinal

fluid. In this stage the serum has appeared to be powerless. I think it is as well, however, even in this stage, to perform occasional lumbar punctures, to know if by any chance diplococci have reappeared in the cerebrospinal fluid, where there would be some hope of good effect from several successive doses. At these times an occasional dose of serum should be given, though little good is to be expected from its use if diplococci are absent.

It is a probability that in some chronic cases there is a condition of chronic hydrocephalus, and it is a question whether this may not be largely responsible for the patient's condition. This would be shown by the fact that at lumbar puncture a considerable amount of fluid is obtained under considerable pressure. When this is the case, I would suggest that the older treatment by repeated lumbar puncture, without the injection of serum, should be tried. The condition is a very serious one and almost the only hope is to keep the pressure reduced as far as possible. I believe that a daily lumbar puncture should be done, withdrawing as much fluid as possible. I cannot base my advocacy of this method on experience, as it has not been used with a sufficient number of cases. In the few cases in which it has been tried no good result appeared. But severe chronic cases are rather hopeless, and I think daily lumbar puncture is worth trying when pressure is high.

MANAGEMENT OF RELAPSES.

In one form of relapse the patients have not become entirely free from symptoms and fever, although they have shown marked improvement before they began to get worse again. The treatment of this form of relapse has been described under prolonged cases, but if the relapse begins while one is waiting four days, treatment should be begun at once. In another form of relapse, a true relapse, the patient has been without fever or important symptoms, when he becomes worse, either by a rise of temperature, a recurrence of symptoms or both. Cases in which a rise of temperature is the only manifestation are not nearly so serious as those in which there is a recurrence of any affection of the mental condition. The latter is quite serious, especially if there is no fever or reappearance of diplococci, and may be the precursor of the unfavorable chronic stage.

The treatment of a true relapse is the same as that of the form described under prolonged cases,—immediate lumbar puncture and injection of full doses of serum, the injections to be repeated as long as diplococci or symptoms persist; or, in the absence of such persistence, until four full doses have been given; or, in the presence of continued symptoms, until the chronic stage is established.

Too much stress cannot be laid upon the necessity of giving several repeated full doses rather than a single one, or smaller ones at all times when the injection of serum is indicated. My experience has led me to believe that this is

especially important in relapses. The cases in my series in which single doses were given in relapses did not do as well as those in which the relapses were combatted by repeated full doses.

SUMMARY OF THE METHOD OF USING ANTI-MENINGITIS SERUM.

1. Perform lumbar puncture, prepared to give the serum as soon as meningitis is suspected. If the fluid is cloudy, give the *first* full dose of serum at once, without waiting for the bacterial examination, although further doses are only to be given in case the diplococcus intracellularis is found in the cerebrospinal fluid. The serum is of no value in other forms of meningitis.

2. At every dose give as much as possible. Always withdraw as much cerebrospinal fluid as possible. Give 30 ccm. in all cases in which the amount of fluid withdrawn is 30 ccm. or less, unless a distinctly abnormal sense of resistance is encountered after as much has been injected as has been withdrawn. In all cases in which the amount of fluid withdrawn is more than 30 ccm., give as much serum as the quantity withdrawn. In very severe or fulminating cases, in which the amount withdrawn is between 30 ccm. and 45 ccm., give 45 ccm. unless abnormal resistance is encountered.

3. In very severe or fulminating cases, repeat within twenty-four hours as soon as the patient begins to get worse again, or at twelve-hour intervals.

4. In average cases, repeat daily, until four full doses have been given in all cases.

5. If diplococci persist after four full doses have been given, continue the injections until they have disappeared.

6. If subjective symptoms, any impairment of the mental condition or fever persist after diplococci have disappeared, or after four full doses have been given without progressive improvement, wait four days if the condition of the patient is stationary. At the end of four days, or at any time if the patient's condition is getting worse, repeat the treatment with four daily full doses, and continue as if this were the original attack.

7. When a relapse occurs, either by reappearance of diplococci in the cerebrospinal fluid or by a reappearance of symptoms, give four daily full doses and continue treatment as if this were the original attack.

8. Treatment along these lines should be continued until the patient is symptom-free, without diplococci in the fluid, or until the chronic stage is established.

9. In the chronic stage, watch for possible reappearance of diplococci by doing occasional lumbar punctures. If diplococci reappear, resume treatment with the serum as outlined above. In chronic cases with excessive cerebrospinal fluid under marked pressure, try daily lumbar puncture without the injection of serum.

The following charts are part of the evidence upon which the above conclusions are based:

EXPLANATION OF THE CHARTS.

Chart 1. A case illustrating the result of too small doses. It was a case of average severity in which injections were begun on the second day. As only small quantities of cerebrospinal fluid were obtained, small doses of serum were given daily for four doses. Symptoms improved but were not completely relieved, and the temperature rose. On the tenth day the patient's con-

dition was worse, and three small doses were given, after which the condition remained stationary. On the twenty-first, twenty-second and twenty-third days, sufficient cerebrospinal fluid was obtained to permit the giving of full doses of 30 ccm. This was followed by rapid permanent relief of the symptoms and fever.

Chart 2. A case in which the serum was given in full doses of 30 ccm. It was a case of the same initial severity as that shown in Chart 1, and in

both, treatment was begun early in the course of the disease. The use of successive full doses was followed by lysis and permanent relief of symptoms.

Chart 3. Illustrating improper use of the serum, both at the outset and after the case became prolonged. At the outset, on the twelfth day, one small dose was given and was followed by no effect. The injections were not repeated until the twenty-eighth day, at which time the disease was still in an active stage. Injections were then begun in full dose and were not repeated on successive days, but strung along at intervals. On the thirty-eighth, thirty-ninth and fortieth days, full doses were given with marked improvement. An additional dose was given on the forty-second day, probably because of an evening rise of temperature, after which recovery was uninterrupted. This chart shows no improvement until the serum was used in successive doses.

Chart 4. In this case the serum treatment was begun on the eleventh day, about the same stage in the disease as in the case shown in Chart 3.

The case was one of greater initial severity than the other, but the injection of four full successive doses was followed by rapid improvement and recovery.

Chart 5. This case illustrates the improper management of relapses. The two first doses of the serum were followed by a marked improvement in the patient's mental condition and subjective symptoms. On the twenty-first day these symptoms became notably worse and one injection of 15 ccm. was given without effect on the symptoms. The patient's condition remained stationary until the twenty-fifth day, when one full dose was followed by a fall of temperature and rapid relief of symptoms. A relapse occurred on the twenty-ninth day, when one injection of 10 ccm. was followed by steady

though slow improvement. I believe that in this case relapses might have been prevented if the serum had been properly used.

Chart 6. A case in contrast to that shown in Chart 5, showing the proper management of a relapse.

CARCINOMA OF THE VERMIFORM APPENDIX, PROBABLY PRIMARY, IN A CHILD NINE YEARS AND ONE MONTH OF AGE.

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We feel that the publication of this case of carcinoma of the vermiform appendix¹ is warranted for the following reasons: It was found in an appendix removed for another cause; it occurred in a child only nine years and one month old, and carcinoma² of the vermiform appendix is comparatively rare.

CLINICAL REPORT. — DR. DAY.

The patient whose symptoms and lesions we are reporting was a nine-year-old school girl of Boston.

Family history. — The child's parents were both

¹ We wish to thank William P. Bolles, M.D., Visiting Surgeon to the Boston City Hospital, to whose service the patient was admitted, for permission to report the case and for the use of the clinical records; and Howard A. Lothrop, M.D., First Assistant Visiting Surgeon to the Boston City Hospital, under whose direction Dr. Day performed the operation.

² The literature on carcinoma of the vermiform appendix will be found in the section on malignant tumors in the chapter on "Neoplasms" in the book of Howard A. Kelly and E. Hurdon on the "Vermiform Appendix and Its Diseases," edition of 1905; and in the papers, "Primary Carcinoma of the Vermiform Appendix, with a Report of Three Cases," Baldauf: Albany Med. Ann., December, 1905; and "Primary Malignant Diseases of the Vermiform Appendix," H. D. Rolleston and Lawrence Jones: Am. Jour. Med. Sc., 1906.

born in Ireland. They have always been well and strong. Her mother is fifty-one years old. She has been married twice. Her first marriage was at the age of fifteen and resulted in 9 normal children, 4 of whom are living and well; the others died in infancy, 2 of scarlet fever, 2 of pneumonia and 1 of bronchitis. The father of these children died of pneumonia. He had always been well and strong previously. The second marriage was twelve years ago. Our patient is the only child.

None of the patient's relatives, so far as can be ascertained, have ever had consumption, heart disease, dropsy, Bright's disease, growths or tumors of any kind. There have been no monstrosities in the family.

The mother has a small mole situated between her breasts. It is flush with the skin, and about 2 cm. in diameter.

Past history. — A 'normally delivered and well-nourished, breast-fed infant, born Oct. 31, 1898. Never ill until first year. She then had "typhoid pneumonia," "gastric fever," "German measles" and "bronchitis," all at the same time. Ill for about two months. Once or twice a year since she has had an attack of nausea and vomiting. Vomitus consisted of a green fluid. These attacks had apparently no relation to food eaten. They would last about one day and disappear after treatment with castor oil. Last attack about six months ago. Mother does not know whether child has lost weight, but thinks that she has not. Has always played about with other children and attended school regularly.

Present illness. — For past two months child has occasionally complained of pain located in right lower abdomen. Mother paid little attention to this. Nov. 6, 1907, our patient had a sudden sharp attack of pain located in the center of her abdomen. This pain is said to have been aggravated by pressure. Child put to bed. She did not vomit, but pain and tenderness increased in severity and finally became localized in right lower quadrant of abdomen. Sent to hospital the following day.

Physical examination. — Fairly well-developed and nourished child. Conscious and rational. Pupils equal and react to light and distance. Tongue protruded straight; has a dry, white coat. Slight enlargement of tonsils. Nothing else abnormal seen in throat. No palpable glandular enlargement. *Heart* normal in area; no murmurs heard. Action rapid and regular. *Lungs:* good resonance and respiration throughout. Knee jerks obtained. All reflexes normal. Temperature, 101.5; pulse, 128; respiration normal.

Local examination. — Patient rather anemic looking, with pinched face. Facial expression suggests peritonitis. Abdomen presents spasm of right side. Well-marked tenderness and spasm in right lower quadrant. No point tenderness; no mass felt. Palpation slightly unsatisfactory on account of its causing pain.

Nov. 7, 1907, ether and operation at parent's request. Usual asepsis. McBurney incision one and one-half inches long made over McBurney's point. Peritoneum opened; three strips of gauze used to wall off the appendicular region. The appendix, found by exploring with finger, was retrocecal and bound down by very firm adhesions. Adhesions carefully separated. The appendix, when made to present in wound, was seen to be acutely inflamed and showed a small perforation in its side from which escaped fecal material. Appendix seized with Oschner clamp. Meso-appendix separated. Meso-appendix and base of appendix tied off together by two catgut ligatures. Appendix cut off about one third of an inch from cecum and re-