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THE PRESENT STATUS OF THE SERUM THERAPY OF EPIDEMIC CEREBRO- SPINAL MENINGITIS *

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My intention is to present a very brief statement of the status of the serum treatment of epidemic meningitis. It is now about three years since the serum was first used therapeutically in this country. Gradually its employment has extended until now it is being used in Great Britain, France and Germany, as well as in the United States and Canada. Indeed, the Rockefeller Institute has sent supplies to India and to Jerusalem, but, as no reports have been received from these distant places, they will not be further considered at present.

At the time of the first employment of the serum in this country the epidemic of meningitis had already receded in the East, and, although the disease spread westward even beyond the Rocky Mountains and was often very severe and fatal, yet the number of cases arising or being recognized in any one community was not large. I, therefore, view the test made of the serum in America as having coincided with the period of recession of the epidemic.

At the period of the first employment of our serum in Belfast and Edinburgh the epidemic was at its height; that is to say, it had reached its maximum development, from which it was tending to recede rather than to extend. All the evidence at hand shows that the disease at that time had not diminished in virulence and fatality, but the number of cases appearing was in a given time less than before.

In Germany, also, the epidemic was virtually at an end when the serum was received. In France, on the other hand, the serum was available at the beginning of the outbreak of the epidemic which is now prevailing in Paris and the provinces. To the fortunate circumstance that Professor Calmette, on his return from the International Congress on Tuberculosis, carried with him to Lille a considerable quantity of the serum is to be ascribed its prompt employment. Subsequently the Rockefeller Institute sent large supplies to him, to Professor Netter and to Professor Roux. The reports of the serum treatment now appearing in French medical journals are based chiefly on the employment of the serum prepared at the Rockefeller Institute.

If, therefore, the decision of the value of the serum treatment was properly withheld until the opportunity arose to subject it to a test at the beginning of a severe

epidemic, when the fatality is commonly at its height, this opportunity has now arrived in France. The outlook is further promising for a comparative study of cases of epidemic meningitis treated with the serum and in other ways. While the serum is being employed widely, apparently, in Paris and in the intense way that experience has indicated to be the best, namely, by successive injections of relatively large doses, in the provinces it is being less generally employed and it has been found difficult to have the intense method carried out by the provincial practitioners. When the reports are all in and the figures have been collected we may expect, therefore, valuable information on the value of the serum.

In the meantime, I can report to you that the excellent results obtained from the serum in America and Great Britain are being repeated in France. There have already been published reports covering 100 or more cases of the disease treated with the serum in which the mortality will probably be less than 25 per cent. On the other hand, a smaller number of cases thus far reported treated by other methods have given a far greater mortality and one approaching 80 per cent. Moreover, the phenomena of diminution in severity of the symptoms and reduction of the period of infection and convalescence have been observed there as elsewhere.

We may, then, consider fairly, I think, that the serum treatment has now been subjected to test under a variety of conditions, some of which were as severe as probably ever occur. And yet I should still advise caution in concluding that the case has been proved for the serum. The total number of reports of cases of epidemic meningitis treated with the serum prepared at the Rockefeller Institute which I have collected is under one thousand, and it obviously will take a larger number than that to establish its value. I wish now to present a tabulation which has recently been prepared based on 712 cases of the disease in which the bacteriologic diagnosis was made and the serum treatment used. In the first table the cases are subdivided according to certain age periods, and in the second the total cases of each age period are further subdivided according as the serum was injected in the three arbitrarily chosen periods of duration of the disease.

TABLE 1.—CASES OF EPIDEMIC CEREBROSPINAL MENINGITIS
TREATED WITH THE ANTIMENINGITIS SERUM

CASES ANALYZED ACCORDING TO AGE GROUPS				
Age years.	Total no. cases.	Recovered.	Died.	% Mortality.
1-2	104	60	44	42.3
2-5	112	82	30	26.7
5-10	113	95	18	15.9
10-15	101	73	28	27.7
15-20	107	72	35	32.7
20+	175	106	69	39.4
Total, all ages	712	488	224	31.4

Table 1 brings out several points of interest. The highest mortality is shown to have occurred in the first

* Read in the Section on Practice of Medicine of the American Medical Association, at the Sixtieth Annual Session, held at Atlantic City, June, 1909.

two years of life. But contrary to the rule under the older forms of treatment in which the mortality was 90 per cent., or over, in this series it was 42.3 per cent. The second age period is from 2 to 5 years, in which the mortality was 26.7 per cent. The third age period embraces children from 5 to 10 years of age and gave the lowest mortality of all, namely, 15.9 per cent. The next period extends from 10 to 15 years and gave a mortality of 27.7 per cent. The next period of from 15 to 20 years showed a considerable rise in mortality, equaling 32.7 per cent., and the last period, embracing the cases of 20 years and over, gave a mortality of 39.4 per cent. The average mortality in all the age periods was 31.4 per cent.

The time allowed me is insufficient to enable me to enter into a detailed discussion of the figures. It is my intention, however, to consider them in some detail in the near future. A point of importance and one to which Dr. Jobling and I have already referred is the importance of experience with the serum in securing the best results from it. If the separate large series of cases treated by individual observers are analyzed, the great discrepancy in the results as between children over 2 years of age, young adults and adults past 20 years are not encountered.

TABLE 2.—CASES OF EPIDEMIC CEREBROSPINAL MENINGITIS TREATED WITH THE ANTIMENINGITIS SERUM
CASES ANALYZED ACCORDING TO DAY OF INJECTION

Ages. Yrs.	1st-3rd			4th-7th			Later than 7th		
	Rec.	Died.	%	Rec.	Died.	%	Rec.	Died.	%
1-2	16	1	5.8	22	10	31.2	22	33	60.
2-5	24	6	20.	40	12	23.	18	12	40.
5-10	43	8	15.6	35	6	14.6	17	4	19.
10-15	36	8	19.	23	9	28.1	14	11	40.
15-20	25	17	40.4	25	8	24.2	22	10	31.2
20+	36	21	36.8	34	24	41.3	36	24	40.
Totals..	180	61	25.3	179	69	27.8	129	94	42.1

Table 2 is instructive in bringing out the importance of early injections of the serum. The results in the first two years of life are especially noteworthy. The extraordinary figures given under the first period of injection, namely, in the first three days of the disease, can hardly be maintained. But the influence of period of injection is shown by the rapid rise in mortality in the subsequent two periods. The rule of the effects of early injection is preserved in the age periods up to the period of from 15 to 20 years, when it disappears. The discrepancy occurring in the two highest age periods cannot be wholly accounted for at present. The explanations which suggest themselves are that among older individuals there tends to be a large number of very severe, rapidly fatal or fulminating cases of the disease, or that older persons are less subject to the beneficial action of the serum. As regards the actual proposition, it may be stated that adults not infrequently respond promptly to the serum injections by abrupt termination of the disease or ameliorated symptoms and pathologic conditions.

The total figures do not, however, fail to indicate that the early injections are more effective than the later ones, as is shown by the percentage mortality in the first-to-third-day period of 25.3, in the fourth-to-seventh-day period of 27.8, and the period later than the seventh day of 42.1.

There is one consideration which I should like to touch on. The study of certain groups of cases of epidemic meningitis, coming under one observer, indicates that the diagnosis can sometimes be made before the usual symptoms of meningeal irritation appear or are recognizable. The cerebrospinal fluid removed by exploratory lumbar puncture has been, in these cases, sometimes clear and sometimes turbid and contained

more or less polynuclear leucocytes and always *Diplococcus intracellularis*. The serum being injected immediately, these cases almost invariably were abruptly terminated or ran relatively a mild course. Attention having been drawn to the cases as being possibly examples of epidemic meningitis because of the similarity of the prodromal symptoms to those of other cases diagnosed later after the signs of meningeal irritation were plain, they ran a short and mild course after the early administration of the serum, while the others, which served to direct the attention, having been injected later when the infection and inflammation were well established, assumed a far more severe and protracted form.

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ABSTRACT OF DISCUSSION

DR. THOMAS MORGAN ROTCH, Boston: In my wards at the Children's Hospital during the last ten years, I have had on an average twenty of these cases each year. The children treated were in the first twelve years of life and I have carried out a different form of treatment during each of the past six years. During 1899, 1900, 1901 and 1902 no special treatment was employed and the mortality varied from 60 to 80

Chart showing death rate from epidemic cerebrospinal meningitis at the Children's Hospital, Boston, from 1899 to 1908.

per cent. During 1903, 1904 and 1905 the treatment was by repeated lumbar punctures and the mortality continued from 60 to over 70 per cent. Although the lumbar punctures produced no notable change in the percentage of deaths yet a certain temporary amelioration was noticed at times. During 1906, all the children were treated with diphtheria antitoxin, the doses varying from 115,000 to 144,000 units according to the age of the child. An analysis of these cases showed no especially favorable results, the mortality being about 80 per cent. During 1907, in connection with my work on the opsonic index the treatment was with the vaccines and the mortality still remained up to about 80 per cent. In all the nine years from 1899 to 1907 the mortality varied from 60 to 80 per cent.

From Nov. 1, 1907, to Nov. 1, 1908, the Flexner serum was employed and the mortality immediately fell from 80 to 19 per cent. This lower rate of mortality has varied a little since Nov. 1, 1908, but has never gone above 25 per cent.

The technic of the serum treatment in these 74 cases has been carried out by Dr. Charles Hunter Dunn. The amount of serum given varied according to the case but from 30 to 45 c.c. at a dose was found to be safe, given daily for at least four days. It is seldom that too much serum is given. In one patient, a small baby, symptoms of cyanosis, irregular respira-

tion and collapse occurred but the symptoms soon passed off and in the Dunn series only one other child was affected and this not seriously.

The mistake which is most likely to be made is the giving of too little rather than too much. It is also a mistake to stop repeating the dose until grave symptoms return. The serum should be repeated at least once a day and in grave cases oftener until not only all symptoms have disappeared, but until the organisms are no longer found in the spinal fluid. Reports as to the results do not give a fair idea of the value of the serum treatment unless the technic is carried out in the most perfected way. In this series of 74 cases the technic was carried out with the greatest precision with the method approved by Flexner.

The serum treatment should not be mistrusted or given up because certain patients do not respond to it. There are two reasons why some individuals do not respond to the serum: 1. Because in some cases it is probable that the serum can not reach certain parts of the brain infected. For instance, if by the inflammatory process brought about by the disease the foramen of Magendie has been closed the organisms may still be active while enclosed in the ventricles where the serum can not reach them or in like manner perhaps in some remote cerebral sulcus. 2. It has not been proved that there are not a number of strains of *Diplococcus intracellularis*, some of which may be resistant to the serum.

In those cases in which an individual does not respond to the serum, cultures from the spinal fluid should at once be sent to the Rockefeller Institute in order that Dr. Flexner should be enabled to investigate this possibility and perhaps later be able to increase the polyvalent property of the serum by including them in immunizing his horses. Analogous to these characteristics of the *Diplococcus intracellularis* is the well-known efficiency of certain strains of the lactic acid bacillus and the uselessness of others on certain fermental saprophytes in the intestine. The truth of these observations has been exemplified in Dunn's clinical work.

DR. PHILIP KING BROWN, San Francisco: Dr. Rotch's statement regarding the care of these patients in hospitals makes me wish to report a brief experience with the treatment of these cases in country towns in California where the disease seems to be endemic. It appears in epidemic form occasionally in small isolated communities. I wish especially to speak of this because of the remarkable results obtained in the use of the serum by the country practitioners and they should be given the credit of the work. I can not allow this opportunity to pass without speaking of it because of its bearing on the general use of the serum which I believe is bound to come. In all but one group of cases the serum was administered by the physician to whom I gave it, after I had made the initial injection. The most striking results occurred in one small town where eleven patients died before the serum was used. Then in a twelfth doubtful case the child recovered. The deaths occurred in periods of from five hours to four days after the onset of the initial symptoms. After the introduction of the serum, three patients promptly recovered. The fourth case died because the supply of serum gave out. A fifth patient from a distant place, ill two weeks before the serum was tried, recovered after the use of a number of doses of the serum. In a number of localities where I have gone to administer the first dose of the serum, I left a supply to be used by the local physician in the further care of patients and in subsequent cases that might arise. The best results obtained in California were obtained by the country doctors. In one late case the patient was deaf and nearly blind when the serum was begun; the sight returned to normal, but the hearing was not recovered. In another case the patient was almost blind before the use of the serum, but the sight was subsequently regained. Strange to say, the results in San Francisco were not so good as in the country towns. I did the work myself and did the best I knew how, but still I was not able to obtain the results obtained by the men in the country. Generally speaking, this seems to have been due to the late use of the serum, to complications and to the very bad hygienic surroundings in the homes of several of the patients. In no case, however, did I have to contend with the

difficulties and disadvantages hygienically and as regards assistance in carrying out the treatment that attended all the cases I saw in the country towns and still my results were not as good as the country physicians'.

DR. WILLIAM LITTERER, Nashville, Tenn.: There has just been an epidemic of cerebrospinal meningitis in Nashville. The number of cases was 20, which was confirmed by bacteriologic examinations. Dr. Flexner kindly furnished us all the serum that we needed. In the first three cases in which the serum was not used, the patients died promptly. Out of the seventeen remaining patients in whom the serum was used, only 7 died; 3 of those who died were practically moribund when the serum was injected. The serum acted like magic on 2 moribund patients. Leaving out the moribund patients, 4 out of the 14 died.

We were particularly struck with two cases in which the meningococci were found in fairly large numbers in the fluid. After the first injection of the serum the number had decreased materially and by the third injection cultures were absolutely negative and the spinal fluid perfectly clear, yet the patients complained of agonizing headaches which were the chief feature of these cases. One of the patients died on the eighth and the other on the sixth day of the disease. I am of the opinion that the meningococci had extended into the ventricles of the brain and that the serum could not reach them. I am further of the belief that possibly we could have saved the patients had we injected the serum into the ventricles of the brain.

DR. SIMON FLEXNER, New York: There are two symptoms which are likely to persist after the disease has entirely yielded to the treatment, namely, rigidity of the neck and the Kernig sign. Other things being favorable, they can be disregarded, and may persist even for several weeks, and gradually disappear. A second point I should like to refer to is that apparently certain strains of the diplococcus are more resistant to the destructive and inhibiting influence of the serum already mentioned. How to explain this I do not know. I had intended to collect some of these strains for a special study, but have had little success in securing them thus far. The cases have occurred often in distant and widely separated places, so that the cultures of the resistant diplococci have not survived the journey by mail to New York, and so far I have not succeeded in securing such resistant strains in New York. I trust to pursue this investigation in the future.

I am confident that the inflammatory exudate is sometimes formed in inaccessible parts of the meninges, or in deeper parts of the brain where the serum can not reach. Then in cases of hydrocephalus the obstruction at the base of the brain often prevents the serum from reaching the cerebral meninges and ventricles, where the exudate is contained. Cushing of Baltimore first carried out intraventricular injection of the serum in children in whom this obstruction existed, after trephining the skull; and in young children it is possible to make the injection through the anterior fontanelle, but up to the present time in no case of this kind, so far as I know, has the patient recovered. Whether better results will be obtained later can not of course be predicted, but in any event I think the operation justifiable, since these cases always terminate fatally.

Finally, I wish to express my deep sense of indebtedness to the large number of physicians, many of whom I have never met, for their hearty cooperation, which I appreciate very much, and without which this wide investigation could not have been made.

Fly Poison.—Formalin, used as a poison for flies, needs to be swallowed by the insect, hence the flies must be attracted to the poison by mixing with it an appetizing food and by spreading the mixture over a large surface. Honey has given poor results. The *Scientific American* says the best mixture is made with milk. It recommends a solution containing 15 per cent. of the formalin of commerce, 20 per cent. of milk, and 65 per cent. of water, placed in large flat vessels. Most of the dead flies fall, not within the vessels, but around them, sometimes at a great distance.