A REPORT ON THE SERUM TREATMENT OF TWENTY-SIX CASES OF EPIDEMIC POLIOMYELITIS.

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INTRODUCTION.

This report describes in some detail the method used and the results attained in twenty-six cases of acute poliomyelitis treated with human serum from recovered and convalescent cases of the disease. The cases were treated during the epidemic which prevailed in the summer and autumn of 1916 in New York State.

The epidemic was attended by a high death rate uniformly affecting large groups of cases occurring in city and suburban localities. In this, as in previous epidemics, the greater number of deaths occurred in those cases in which the upper portions of the spinal cord were involved, or in which an ascending, or Landry's type of paralysis occurred. The percentage of deaths from secondary causes, such as pneumonia, was small. Aside from this, no secondary or metastatic foci of infection, outside the central nervous organs, arose or were detected. This fact should be mentioned in connection with the claims that have been made that epidemic poliomyelitis is a form of streptococcus infection.[1]

At the onset the disease may offer a perplexing problem to the attending physician or expert diagnostician. In both the field and ward work at the Westchester Isolation Hospital use was made of lumbar puncture and microscopic and chemical examinations of the cerebrospinal fluid at the bedside in order to arrive at a rapid differential

[1] Mathers, G., *J. Infect. Dis.*, 1917, xx, 113. Rosenow, E. C., Towne, E. B., and Wheeler, G. W., *J. Am. Med. Assn.*, 1916, lxvii, 1202. Nuzum, J. W., and Herzog, M., *J. Am. Med. Assn.*, 1916, lxvii, 1205.

diagnosis. In addition to detecting two cases of epidemic cerebrospinal meningitis which quickly yielded to injections of the antimeningococcic serum, and one case of acute meningitis due to a bacillus probably belonging to the paracolon group, the procedure commended itself especially as it enabled us, first, to remove to the hospital cases on the 1st or 2nd day of illness, thereby contributing materially to the efficiency of the isolation, and, next, to bring under the specific serum treatment cases in the earlier stages of the affection. The groups of histories given show the advantages of the latter point, but it is mentioned here since it has been proved feasible, in field work in country districts, to take the necessary apparatus to the bedside and to make a diagnosis immediately by means of lumbar puncture and clinical examinations. Valuable time may be lost if the fluid is sent to the laboratory, and in the most perplexing cases the diagnosis can be made only by considering the character of the cerebrospinal fluid, as revealed by microscopic and chemical examination, in connection with the clinical findings at the time the fluid is withdrawn. In some cases, though rarely, it may be necessary to repeat the lumbar puncture in 6 hours.

HISTORICAL.

The discovery, almost simultaneously by Flexner and Lewis[2] and Landsteiner and Levaditi,[3] of the filterable nature of the microorganism, or virus, causing the disease, was quickly followed by Flexner and Lewis's[4] observation that recovery from an attack of experimental poliomyelitis afforded protection to a second inoculation; and this in turn was followed by the detection of immunity or neutralizing substances in the blood serum first of recovered monkeys and then of recovered human beings.[5] Since recovery from an attack of poliomyelitis was obviously brought about through a process of immunization, similar to that in other infectious diseases, Flexner and Lewis[6] endeavored to prevent the development of the

[2] Flexner, S., and Lewis, P. A., *J. Am. Med. Assn.*, 1909, liii, 2095.

[3] Landsteiner, K., and Levaditi, C., *Compt. rend. Soc. biol.*, 1909, lxvii, 592.

[4] Flexner and Lewis, *J. Am. Med. Assn.*, 1910, liv, 45.

[5] Levaditi and Landsteiner, *Compt. rend. Soc. biol.*, 1910, lxviii, 311. Römer, P. H., and Joseph, K., *Münch. med. Woch.*, 1910, lvii, 568. Flexner and Lewis, *J. Am. Med. Assn.*, 1910, liv, 1780. Anderson, J. F., and Frost, W. H., *J. Am. Med. Assn.*, 1911, lvi, 663.

[6] Flexner and Lewis, *J. Am. Med. Assn.*, 1910, liv, 1780.

infection in inoculated monkeys through the administration of blood serum taken (*a*) from recovered monkeys and (*b*) from recovered human beings. The results, while not constant and regular, were definite. The method pursued by Flexner and Lewis was first to make an intracerebral inoculation of the active adapted monkey virus, and then, about 24 hours later, to begin treatment by intraspinal injections of the immune serum. Their results were prevention of the onset of paralysis in some cases, and delay of the onset in others. Account should be taken, however, of the high potency of the adapted virus and the mode of its inoculation since the number of infections following was 100 per cent and the mortality among the paralyzed animals nearly as high. The experimental disease is, therefore, far more severe than the corresponding epidemic condition in man; and presumably it is less subject to favorable influence through therapeutic measures.

These experimental results were at once utilized as a basis of a serum therapy in man.[7] Netter and his associates[8] have reported a total of thirty-four cases of acute poliomyelitis which they have treated by the subdural method of injecting immune serum. They have undoubtedly established the fact that, as in the monkey, subdural injections intelligently carried out in man are safe. They believe further that they have proved them to be definitely beneficial or curative. They became increasingly convinced that the period of the disease at which the injections were made counted vitally, and they urged that the injections should be made as early as possible in the course of the infection.

During the past summer the serum treatment has been carried out in a number of different hospitals. Very few reports giving the circumstances and details of the methods and results have thus far appeared. But a number of important facts bearing on the subject have been acquired from clinical observation and experimental study. In the first place, a meningitis accompanied by a pleocytosis precedes in many instances the onset of paralysis. It is, therefore, one of the particular tasks of the attending physician to detect the disease in this early period when the treatment offers the greatest possibility of benefit. In the second place, the meningitis is attended by an increased permeability of blood vessels in the inflamed pia arachnoid. By reason of this increased permeability, it is possible for protein and other substances introduced into the blood to reach the subarachnoid spaces and probably the perilymphatic spaces in the nervous organs

[7] Netter, A., Gendron, A., and Touraine, *Compt. rend. Soc. biol.*, 1911, lxx, 625.

[8] Netter, A., *Bull. Acad. méd.*, 1915, lxxiv, series 3, 403. Netter, A., and Salanier, M., *Bull. et mém. Soc. méd. hôp. Paris*, 1916, xl, series 3, 299.

which are otherwise excluded. Hence, while the most direct route to the perivascular lymphatic and perineural spaces in the spinal cord may still be by way of the cerebrospinal fluid, this is not the only way since a blood route is also available. This blood route may lead directly to the interstices of the nervous tissues. Flexner and Amoss[9] ascertained that an aseptic meningitis set up by an intraspinal injection of horse serum opened the way to the nervous tissues for the virus of poliomyelitis introduced into the blood, often leading to infection and paralysis which a blood injection alone does not accomplish. These authors[10] also report that after the subdural injection of horse serum, immunity principles passively introduced into the blood pass into the cerebrospinal fluid. These facts indicate that in endeavoring to influence the course of epidemic poliomyelitis in human beings, the following conditions should be observed: (1) early and prompt diagnosis and treatment; (2) intraspinal injection of immune serum; (3) injection of immune serum directly or indirectly into the blood. The coincident injection into the blood is indicated not only by the pathology of poliomyelitis but also by the physical phenomena involved, since it may be assumed that the tendency will be for an equilibrium to be established between the serum in the subarachnoid space and that in the blood. Increasing directly the serum in the blood should diminish the rapidity of outflow of that in the meninges. It happens fortunately that protein substances introduced into the low levels of the subarachnoid spaces pass into the blood more slowly than when introduced at higher levels.[11] Furthermore, it is possible to administer larger amounts of serum by the blood than intraspinally. Finally, the serum employed should be collected from cases which have recently passed through an attack of poliomyelitis, and not many years after, as has been the practice of Netter and others. It is to be supposed that the serum will contain a greater amount of immune substances in this early period than after the lapse of many years. A test carried out with a sample of blood serum taken from a patient on the 6th day of illness showed that it already contained the neutralizing principles.[10]

[9] Flexner, S., and Amoss, H. L., *J. Exp. Med.*, 1914, xx, 249.

[10] Flexner and Amoss, *J. Exp. Med.*, 1917, xxv, 499.

[11] Dixon, W. E., and Halliburton, W. D., *J. Physiol.*, 1915–16, l, 198.

CASE HISTORIES.

The serum employed in the series of cases to be reported was obtained from human beings who had recently recovered from an attack of epidemic poliomyelitis and who, at the time the serum was taken, were still paralyzed. All the donors of the serum except two had been convalescent for 8 weeks or less. The two exceptions had passed through the disease 2 years before.

The use of the serum from recently recovered persons, otherwise healthy, involves no risk of transferring the microorganism of poliomyelitis. In the first place, the virus has never been detected in the circulating blood of human beings even in the first days of the disease.[12] In the second place, even if minimal quantities of the virus are present in the circulating blood, the presence of the immunity principles in the serum would bring about its neutralization during the 48 hour period following the collection of the serum, during which sterility is being determined prior to its use.

The serum administered was collected under aseptic conditions, and was used uninactivated and unpreserved. The conditions surrounding the treatment of this series of cases were so carefully controlled that no risk was taken. On the other hand, one can now state that inactivation of the serum by heating to 53°C. for $\frac{1}{2}$ hour or by the addition of 0.2 per cent tricresol does not impair the protective power.

Mode of Administration.—For the reasons given, we departed from the methods formerly employed and injected the serum not only intraspinally but also into the blood. The quantity of serum which can safely be given to a child by intraspinal injection within a 12 hour period is obviously limited. In order to increase the quantity of immune bodies present in the fluids and tissues, even larger quantities were injected intravenously directly, or indirectly by way of the skin. The accompanying tables, although based on a relatively small number of cases, indicate the advantage of the larger volumes of serum administered. Some degree of selection was exercised in choosing cases for the treatment. The quantity of available serum was limited, and in view of the unproved value of the serum it was used in those

[12] Clark, P. F., Fraser, F. R., and Amoss, H. L., *J. Exp. Med.*, 1914, xix, 223.

cases in which the fever had not lasted over 48 hours; in a few instances the serum was given to patients who were critically ill, although the febrile period was of much longer duration.

For purposes of analysis and comparison, the cases treated with serum may be divided into two groups. The first group comprises the cases in which some degree of paralysis existed before the serum was administered; the second group includes the cases in which at the beginning of the treatment no paralysis could be detected by physical examination. The cases in the second group, however, were instances of poliomyelitis, since the clinical histories, general findings, and changes in the cerebrospinal fluid left no doubt on that point.

The first group of cases should be further subdivided into two classes: of these one class was under observation long enough for us to determine that the pathologic process in the spinal cord was extending and involving other regions; in the other class treatment was begun immediately in the home and continued after admission to the hospital. No information was, therefore, available to indicate whether the progress of the disease had already become arrested or not.

Group I. Cases Showing Paralysis at the Beginning of the Treatment. Class I. Paralysis Extending.

Case 1.—Male; age 33 years.

Sept. 2, 1916. Malaise, headache, and vomiting. Sept. 3. Unable to bear weight on legs. Sept. 4. Admitted to hospital. Legs completely paralyzed. No tendon reflexes. Cerebrospinal fluid shows 280 cells per c.mm. and increased globulin. Bladder, bowels, diaphragm, abdominal and thoracic walls, and upper extremities normal. Sept. 5. Bladder paralyzed; no abdominal movement during respiration; using accessory muscles of respiration; deltoids weak; cyanosis.

On Sept. 5, 10 cc. of serum were injected intraspinally and 20 cc. intravenously. The cyanosis gradually increased, and death resulted from respiratory paralysis 10 hours after the injection. No obvious influence on the course of the disease was exerted by the serum.

Case 2.—Female; age 10 years.

Sept. 22, 1916. Headache, nausea, fever, and abdominal pain. Sept. 23. Temperature 103°F. Pain in back and in right leg; drags right foot. Sept. 25. Admitted to hospital. Temperature 102.6°F.; pulse 112; respirations 30. Neck and back muscles stiff; flaccid paralysis of both legs; bladder functions. Sept. 26, 6 p.m. Left deltoid paralyzed; dyspneic; employs accessory muscles of respira-

tion; no respiratory movement of abdominal wall; bladder paralyzed. Cerebrospinal fluid contains 270 cells per c.mm.; globulin increased.

On Sept. 26, 20 cc. of serum were given intraspinally and 60 cc. subcutaneously. Sept. 27, 8 p.m. Temperature 99.8°F.; pulse 102; respirations 30. Abdominal muscles move with respiration. Sept. 28. Abdomen moves freely; left deltoid responds but not yet normally; bladder inactive. Sept. 30. Bladder acting; no change in leg condition.

The history of the acute stage of this case readily divides itself into two periods. The first (a) takes in the time up to and including the paralysis of the legs, followed by a brief interval when (*b*) the abdomen, diaphragm, shoulder, and bladder became paralyzed. It was during the second period that the serum was administered. Coincidently with the administration there was no further progress, but rather a rapid recession of the recent paralysis; the older paralytic condition was not obviously affected. Whether the phenomena described are of the nature of cause and effect cannot certainly be determined.

Case 3.—Male; age 3 years.

Sept. 26, 1916. Fever and vomiting. Sept. 27. Difficulty in swallowing. Sept. 28. Admitted to hospital. Temperature 101°F.; pulse 112; respirations 38. Paralysis of muscles of deglutition. Sept. 29. Complete paralysis of right side of face. 12 m. Temperature 104.2°F.; pulse 138; respirations 62. Very ill. 2 p.m. Cerebrospinal fluid, 208 cells per c.mm.; globulin slightly increased.

On Sept. 29, 15 cc. of serum were administered intraspinally, 20 cc. intravenously, and 40 cc. subcutaneously. Sept. 30. Temperature 99°F.; pulse 102; respirations 68. Marked improvement in general condition but no change in the degree of paralysis of the face or muscles of deglutition. Before discharge the paralysis had almost disappeared.

Whether the prompt subsidence of the severe general symptoms in this case is to be ascribed to the serum treatment cannot be stated positively. The fact that no extension of the paralysis occurred in spite of the severe symptoms may or may not have been due to the treatment. But in this instance, as in Case 2, the paralysis was extending at the time the serum was given and no further extension occurred. It is obvious that in the first case of this series, no result was accomplished. It should be mentioned, however, that as compared with the more energetic treatment subsequently employed that case received a very small quantity of the serum, which was administered late in the course of the disease.

Class II. Paralysis Present.

Case 4.—Female; age 33 years.

Oct. 16, 1916. Chilly sensations; abdominal pain; difficulty in walking. Oct. 17. Stiffness of neck; legs weak. Oct. 18. Admitted to hospital. Temperature 103°F.; pulse 104; respirations 34. Neck and back stiff; weakness of muscles of abdomen and left leg. None of the muscle groups are completely paralyzed. Cerebrospinal fluid, 50 cells per c.mm.; globulin increased.

On Oct. 18, 20 cc. of serum were given intraspinally and 50 cc. intravenously. Oct. 19. Paralysis stationary. Oct. 21. Temperature 99.6°F. No extension of the paralysis.

The serum was administered in this case probably within 24 hours of the onset of definite paralysis, but whether or not it influenced the progress cannot be stated.

Case 5.—Male; age 2 years.

Sept. 13, 1916. Fever and headache. Sept. 18. After an apparently normal interval, vomiting occurred and the neck and back became stiff. Sept. 20. Weakness of legs noticed. Admitted to hospital. Temperature 98.2°F.; pulse 108; respirations 44. Neck and back stiff; face slightly asymmetrical; abdominal wall relaxed; no reflexes; partial paralysis of muscles of legs. Cerebrospinal fluid, 37 cells per c.mm.; globulin increased.

On Sept. 20, 5 cc. of serum were given intraspinally and 30 cc. subcutaneously. The paralysis did not extend, but there was no immediate improvement of the paralyzed muscles.

The treatment in this case was given probably at the end of the 4th day of illness at a time when the paralysis had already been arrested. Apparently nothing definite was accomplished. Case 6, a sister of this patient, should be used for comparison.

Case 6.—Female; age 4 years.

Sept. 19, 1916. Fever, headache, and constipation. Sept. 20. Temperature 101.4°F.; vomiting. Facial asymmetry. 11 p.m. Admitted to hospital. Temperature 102°F.; pulse 140; respirations 32. Neck and back stiff; slight left facial paralysis; weak hamstring and quadriceps muscles on both sides; knee jerks and Achilles tendon reflexes increased. Cerebrospinal fluid cloudy and contains 920 cells per c.mm.; globulin increased.

On Sept. 20, 10 cc. of serum were given intraspinally and 25 cc. subcutaneously. Sept. 22. No extension of paralysis. Sept. 23. Temperature normal.

In this case the serum was given within 30 hours of the onset of the symptoms and at a time when weakness of the muscles of the thighs

was appearing. The temperature became normal in about 60 hours and no extension of the paralysis ensued (Text-fig. 5). Within 2 weeks recovery of all the weak muscles was complete. The striking point in the case is the large number of cells in the cerebrospinal fluid when the serum was injected.

Case 7.—Female; age 2 years.

Sept. 12, 1916. Headache and fretfulness. Sept. 14. Admitted to hospital. Temperature 101.8°F.; pulse 124; respirations 28. Weakness of flexors and extensors of right hip and of gastrocnemius. Achilles tendon reflexes absent. Cerebrospinal fluid contains 99 cells per c.mm. and increased globulin.

On Sept. 14, 5 cc. of serum were injected intraspinally and 30 cc. subcutaneously. Sept. 15. Temperature normal; paralysis stationary. There was never any extension, but gradual improvement of the partially paralyzed muscles. The temperature curve is shown in Text-fig. 1.

Case 8.—Male; age 22 months.

Sept. 9, 1916. Child ill. Sept. 10. Admitted to hospital. Temperature 102.6° F.; pulse 136; respirations 36. Weakness of left quadriceps anterior.

On Sept. 10, 5 cc. of serum were administered intraspinally at home before removal to the hospital. Sept. 11. Left thigh muscles weaker. 20 cc. of serum given subcutaneously. Sept. 13. Temperature normal. Partial paralysis unchanged.

Case 9.—Female; age 3 years.

Oct. 12, 1916. Child feverish and irritable. Oct. 14. Left leg partially paralyzed. Oct. 15. Admitted to hospital. Temperature 99.8°F.; pulse 120; respirations 32. There is stiffness of the neck and back, weakness of the extensors of the left foot, and toe-drop. Cerebrospinal fluid contains 115 cells per c.mm.; globulin increased.

On Oct. 15, 15 cc. of serum were injected intraspinally and 40 cc. subcutaneously. The temperature fluctuated irregularly between 98.6° and 100° F. for 2 weeks. The weakness of the foot and leg increased somewhat. 1 month later some degree of impairment was present in the left quadriceps, hamstrings, peroneals, and toe extensors, while the anterior tibial group was completely paralyzed.

The serum was injected in this case within about 72 hours of the first appearance of any symptoms and at a time when only slight and limited paralysis existed. Nevertheless, the muscular impairment progressed slowly in the muscles first affected and into neighboring muscles, but the degree of paralysis never became severe.

Case 10.—Male; age 15 months.

Sept. 9, 1916. Child feverish and sweating; vomited. Admitted on same day. Temperature 99.6°F.; pulse 132; respirations 36. The neck and back are stiff

and there is doubtful weakness of the right deltoid. Cerebrospinal fluid shows 30 cells per c.mm.; globulin increased.

On Sept. 9, 5 cc. of serum were given intraspinally. There was no further involvement of the right deltoid and the temperature remained normal during the stay in the hospital.

This child was seen within a few hours of the onset of the first symptoms and the serum injection was given at the home before removal to the hospital. No paralysis developed.

Case 11.—Female; age 2 years.

Sept. 27, 1916. At noon the child was feverish. 10 p.m. Stiffness of the neck and back, weakness of the left quadriceps and peroneal muscles, and slight weakness of the intercostals. The patient, whose brother was already in the hospital, was admitted at once. Temperature 101°F.; pulse 110; respirations 32. Cerebrospinal fluid, 30 cells per c.mm; globulin increased.

On Sept. 27, 10 cc. of serum were given intraspinally and 30 cc. subcutaneously. Sept. 28. After 24 hours the temperature was 100°F.; no extension of muscular weakness. Sept. 29. Temperature normal. Muscular impairment gone. No abnormality on discharge.

The serum was administered to this child within 12 hours of the first appearance of the symptoms, and although a degree of weakness of certain muscles was already present, it quickly disappeared.

Case 12.—Male; age 3½ years.

Sept. 12, 1916. Headache and fever. Sept. 13. Temperature 103.8°F. Stiffness of neck and back; weakness of muscles of right ankle; toe-drop. Cerebrospinal fluid, 250 cells per c.mm.; globulin increased.

On Sept. 13, 10 cc. of serum were injected subdurally and 40 cc. subcutaneously. Sept. 14. Temperature 99.6°F. Weakness of muscles diminished rapidly.

The serum was administered within 24 hours of the onset of symptoms and at a time when several muscle groups were impaired. The temperature quickly fell to normal and the muscular weakness soon disappeared.

In considering Cases 1 to 12 the points that can be made definitely are: (1) the diagnosis was clearly established in each; (2) there was some grade of paralysis present in each; and (3) with the exception of Cases 1, 8, and 9, there was either no increase of the existing muscular weakness or paralysis, or there was prompt improvement in these conditions.

Group II. No Paralysis at the Time of Treatment.

In the following series of fourteen cases, no paralysis was detected up to the time that the serum was administered. One reservation should, however, be made: in the early stages of the disease, some of the patients were too ill to warrant a full examination of all the muscle groups and hence a degree of weakness or paralysis may have sometimes been overlooked. Moreover, the quantity of serum administered varied considerably, depending upon circumstances. The cases will be considered in the order of the amounts of serum given.

Case 13.—Male; age 8 years.

Sept. 19, 1916. Headache, fever, and drowsiness. Sept. 20. Same condition; neck and back stiff. Sept. 21. Admitted to hospital. No paralysis detected. Temperature 102.5°F.; pulse 102; respirations 32. Cerebrospinal fluid, 850 cells per c.mm.; globulin increased.

On Sept. 21, 5 cc. of serum were given intraspinally and 15 cc. subcutaneously. Sept. 24. Temperature normal. In the interim weakness of the following muscle groups developed: deltoids, pectorales major, rotators (outward) of arms, flexors of hip, quadriceps and hamstrings, and abdominal wall.

The serum was administered within 48 hours of the onset of symptoms. The amount given intraspinally was small. Weakness subsequently developed in many muscle groups, but in none was the paralysis complete.

Case 14.—Male; age 19 months.

Sept. 19, 1916. Vomiting, attributed to improper food. Sept. 20. Fever; neck and back stiff; muscular twitchings. Admitted to hospital. Temperature 103°F.; pulse 124; respirations 32. While there was muscular stiffness, no weakness was detected. Cerebrospinal fluid, 120 cells per c.mm.

On Sept. 20, 5 cc. of serum were injected intraspinally and 20 cc. subcutaneously. The fever persisted, and paralysis developed, involving ultimately the muscles of respiration. Sept. 23. Died.

Obviously no influence on the course of the disease was exerted by the serum. The experience gained later now indicates that the injection should have been repeated.

Case 15.—Female; age 4 years.

Sept. 23, 1916. Fever and headache; irritable. Sept. 24. Neck and back stiff; muscular twitching. Admitted to hospital. Temperature 103.6°F.; pulse

128; respirations 34. No muscular impairment detected. Cerebrospinal fluid, 360 cells per c.mm.; globulin increased.

On Sept. 24, 10 cc. of serum were given intraspinally and 20 cc. subcutaneously. Sept. 25. Flaccid paralysis of right arm and shoulder girdle with rapid extension and involvement of muscles of respiration. Died.

Autopsy showed severe poliomyelitic lesions of the cervical cord and medulla.

Obviously this case was not benefited by the serum injection, since paralysis developed a few hours after the treatment and extended rapidly.

Case 16.—Female; age 8 years.

Sept. 23, 1916. Headache; restless. Sept. 24. Temperature 102°F. Neck stiff. Cerebrospinal fluid, 730 cells per c.mm.; globulin increased.

Within 6 hours of the onset 10 cc. of serum were administered intraspinally and 20 cc. subcutaneously. The temperature fell slowly and reached normal on the 4th day. During this period weakness of the muscles of both arms and possibly slight weakness of the left leg appeared; complete paralysis was never present. Improvement was rapid, and almost complete recovery of lost strength was made in a short time.

Case 17.—Female; age 2 years.

Sept. 17, 1916. Fever; drowsy; muscular twitching; convulsions. Sept. 19. Admitted to hospital. Cerebrospinal fluid, 60 cells per c.mm.; globulin increased. Temperature 104.2°F.; pulse 132; respirations 32. Neck and back stiff; no muscular weakness.

On Sept. 19, 6 cc. of serum were given intraspinally and 25 cc. subcutaneously. Within 24 hours the temperature was normal. No muscular weakness developed.

Case 18.—Male; age 5 years.

Sept. 14, 1916. Temperature 103°F.; headache; drowsy. Sept 15. Neck and back stiff. Temperature 104°F. Admitted to hospital. Temperature 103.4°F.; pulse 126; respirations 50. No weakness of muscles. Cerebrospinal fluid, 379 cells per c.mm.; globulin increased.

Within 24 hours of the onset 5 cc. of serum were given intraspinally and 25 cc. subcutaneously. Sept. 16. Temperature 101°F. 5 cc. of serum were introduced intraspinally. Cerebrospinal fluid, 249 cells per c.mm. Sept. 17. Temperature normal. No muscular weakness ever developed.

Case 19.—Male; age 4 years.

Sept. 17, 1916. Temperature 102°F.; pain in back. Sept. 18. Temperature 102.4°F. Neck and back stiff. Cerebrospinal fluid, 150 cells per c.mm.; increased globulin. Admitted within 24 hours of onset.

On Sept. 18, 10 cc. of serum were injected intraspinally and 25 cc. subcutaneously. 15 hours later the temperature became normal. No muscular weakness developed.

Case 20.—Male; age 13 months. Cousin of Case 19.

Sept. 17, 1916. Drowsiness and fever. Sept. 18. Cerebrospinal fluid clear and contains 75 cells per c.mm.; globulin increased. The patient was given 10 cc. of serum subdurally and was shortly afterwards brought to the hospital. On admission, temperature 101.4°F.; pulse 120; respirations 26.

Immediately after admission a subcutaneous injection of 25 cc. of serum was given. The temperature rose to 104°F. and fell to normal 22 hours afterwards. There was no subsequent weakness or paralysis.

This patient was treated about 18 hours after the first symptoms. The temperature previous to treatment is not known. After a rise to 104°F. the temperature fell rapidly, reaching normal about 22 hours after the first injection (Text-fig. 2). The child developed no subsequent weakness or paralysis.

Case 21.—Female; age 3½ years.

Sept. 3, 1916. Headache; temperature 102°F. Sept. 4. Temperature 104°F. Sept. 5. Temperature 101.5°F. Stiffness of neck. Sept. 6. Cerebrospinal fluid clear and contains 230 cells per c.mm.; globulin increased. Admitted to hospital the same afternoon. On admission, temperature 102.4°F.; pulse 130; respirations 42. Stiffness of neck and back; no weakness or paralysis noted.

Immediately after admission 5 cc. of serum were injected subdurally and 40 cc. subcutaneously. Temperature reached normal 32 hours after treatment. No definite weakness or paralysis developed subsequently.

In this case treatment was begun about 3 days after the initial symptoms and at a time when paralysis had not appeared. Treatment was followed by a rapid drop in temperature and no weakness or paralysis developed during the period of observation.

Case 22.—Female; age 3½ years.

Oct. 7, 1916. Fatigue, irritability, and vomiting. Oct. 8. Fever and a mild delirium. Oct. 10. Fever persisted; drowsiness. Admitted to hospital. On admission, temperature 101.6°F.; pulse 132; respirations 28. Stiffness of neck and back. Clear cerebrospinal fluid with 88 cells per c.mm.

On Oct. 10, 20 cc. of serum were injected subdurally and 30 cc. subcutaneously. Temperature rose to 104°F. that night and there was slight nystagmus. Lumbar puncture yielded a slightly turbid fluid under considerable pressure. About 30 cc. of fluid were withdrawn from the spinal canal. On the following morning the nystagmus had disappeared and 36 hours after treatment the temperature reached normal. Cultures of the turbid fluid were sterile. Turbidity was due to the presence of a large number of polymorphonuclear leukocytes. No weakness or paralysis developed subsequent to treatment.

This patient was treated 3 days after the initial symptoms when there was no evidence of weakness or paralysis. Following the treatment there was evidence of increased irritation of the meninges and increased pressure in the subdural space which was relieved by lumbar puncture and withdrawal of fluid. The temperature reached normal 36 hours after the injection and the child did not develop any weakness or paralysis subsequently. The serum used in this case contained considerable fat; whether or not this played a part in the reaction following the injection cannot be stated definitely. This was the only instance in which any such reaction was obtained, although other cases were treated with portions of the same serum.

Case 23.—Male; age 5 years.

Oct. 3, 1916. Vomiting. Oct. 4. Fever; vomiting persisted. Clear cerebrospinal fluid with 250 cells per c.mm. Admitted to hospital. On admission, temperature 101°F.; pulse 130; respirations 30. Stiffness of neck and back; no weakness or paralysis.

15 cc. of serum were immediately given subdurally and 40 cc. subcutaneously. Temperature rose to 103°F. and fell to normal 12 hours later. There was no subsequent weakness or paralysis.

This patient was treated about 30 hours after what seemed to be the initial symptoms. At the time of treatment there was no demonstrable involvement of any muscle group. The temperature dropped to normal 12 hours after treatment and the child did not show any weakness or paralysis at any time.

Case 24.—Female; age 1½ years.

Oct. 11, 1916. Temperature 101°F. Oct. 12. Stiffness of the neck and back with muscle tenderness. Temperature 103°F. No demonstrable weakness. Admitted to hospital. On admission, temperature 103°F.; pulse 118; respirations 28. Clear cerebrospinal fluid with 40 cells per c.mm.; globulin increased.

On Oct. 12, 25 cc. of serum were injected subdurally and 35 cc. subcutaneously. Temperature dropped to normal within 16 hours after treatment. At no time was there any demonstrable weakness present.

This patient was treated about 30 hours after the mother first noticed fever, and at a time when there was no demonstrable weakness of any muscles. The temperature became normal in less than 24 hours after treatment (Text-fig. 3). An older sister of this patient was admitted to the hospital on the day previous to the one on which

this case was admitted. The sister had been sick for a period of 4 days with temperature as high as 104°F. She was admitted at the end of the febrile period, 4 days after the onset, and at the time of admission lumbar puncture showed the presence of a clear fluid with 76 cells and increased globulin. She received no serum and developed no weakness or paralysis.

Case 25.—Male; age 5 years.

Oct. 5, 1916. Irritability and fever. Oct. 6. Fever persisted; constipation. Oct. 7. Admitted to hospital. On admission, temperature 103°F.; pulse 104; respirations 28. Marked stiffness of neck and back; active reflexes; positive Kernig. No demonstrable weakness of any muscle group. Clear cerebrospinal fluid with 260 cells per c.mm.; globulin increased.

On Oct. 7, 22 cc. of serum were given subdurally and 45 cc. subcutaneously. The temperature fell to normal within 22 hours after treatment and the patient did not develop any weakness or paralysis.

This patient was treated about 48 hours after onset of the first symptoms and within 22 hours after treatment the temperature was normal (Text-fig. 4). No weakness or paralysis developed. A younger sister of this patient was admitted to the hospital 2 days previously with flaccid paralysis of both lower extremities. In this case onset had occurred 5 days before admission and the temperature had fallen to normal and paralysis had already set in when she was admitted.

Case 26.—Male; age 23 years.

Dec. 9, 1916. Vomiting and headache. Stiffness of neck, hyperesthesia, and asymmetry of patellar reflexes. Kernig's sign present on right side. Temperature 101°F. No demonstrable weakness of any muscle group. Clear cerebrospinal fluid with 40 cells per c.mm.; globulin increased.

38 hours after onset the patient received 20 cc. of serum subdurally and 100 cc. intravenously. Following treatment the temperature fell to normal within 48 hours, the hyperesthesia disappeared within that time, and no paralysis or weakness developed.

This patient, an adult, was treated within 38 hours after the initial symptoms appeared, at a time when there was no demonstrable involvement of the muscles. The temperature rapidly fell to normal, and no weakness or paralysis developed subsequently.

The more important facts relating to the twenty-six cases described are collected in Table I.

TABLE I.

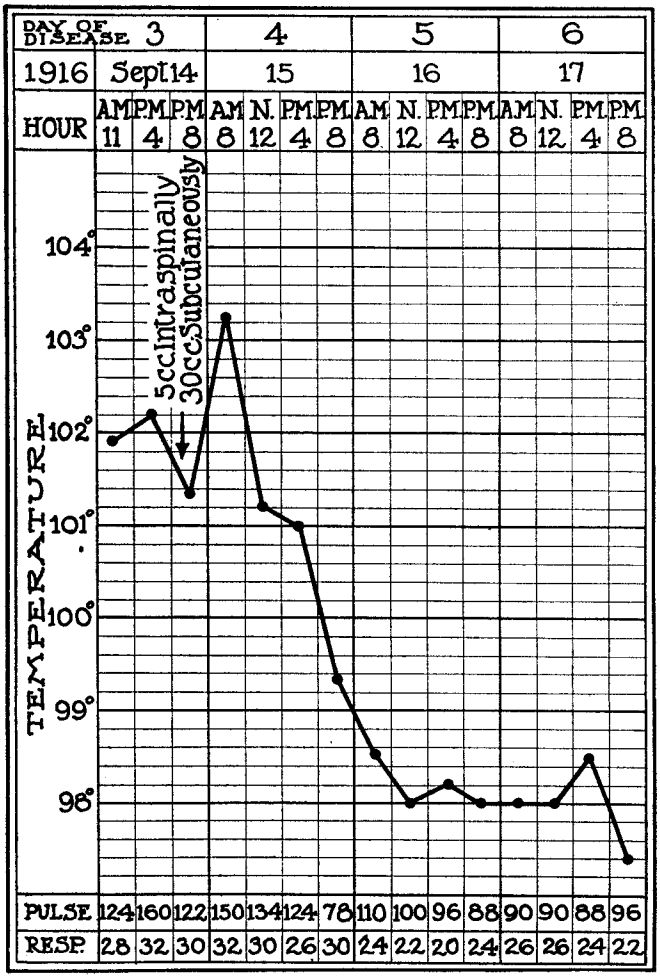
Summary of Cases That Received Serum Treatment.

Case No.	Age.	Clinical condition.	Spinal fluid.		Time between onset of disease and treatment.	Serum administration.			Temperature before treatment.	Time between treatment and normal temperature.	Total amount of serum given.	Result.
			No. of cells.	Globulin.		Subdural.	Subcutaneous.	Intravenous.				
	yrs.				*hrs.*	*cc.*	*cc.*	*cc.*	*°F.*	*hrs.*	*cc.*	
1	33	Ascending paralysis of legs, bladder, and abdominal and thoracic muscles.	280	++	72	10		20	101.2		30	Died 10 hrs. after treatment.
2	10	Ascending paralysis of legs, bladder, abdominal wall, diaphragm, left deltoid, and right facial muscles.	270	++	96	20	60		101.4	24	80	Deltoid and diaphragm functioning 24 hrs. later. Voided 4 days later.
3	3	Right facial and deglutition muscles paralyzed.	208	+	72	15	40	20	104.2	18	75	No further progress of paralysis. Subsequent improvement marked.
4	33	Weakness of left leg and abdominal muscles.	50	+	54	20		50	103.0	60	70	No progress of paralysis. Subsequent improvement.
5	2	Weakness of sternocleidomastoids, both legs, and intercostals.	37	+	96	5	30		98.2		35	No essential change.
6	4	Partial paralysis.	920	++	30	10	25		102.0	60	35	" increase. Complete recovery rapid.
7	2	Weakness of flexors of right thigh.	99	+	48	5	30		101.4	24	35	No progress of lesion. Subsequent improvement.
8	$1\frac{9}{12}$	Weakness of left quadriceps.			48	5	20		102.0	48	25	Slight increase in weakness.

9	3	Weakness of left anterior tibialis.	115	+	72	15	40		100.2	Low fever for 2 wks.	55	Definite increase in extent of paralysis of left leg.
10	$1\frac{8}{12}$	Weakness of right deltoid.	30	++	24	5			101.0	24	5	No increase in weakness.
11	2	Weakness of left peroneal and quadriceps and slight weakness of intercostals.	30	±	12	10	30		101.0	30	40	" " " paralysis. Rapid disappearance of weakness noted on admission.
12	$3\frac{1}{2}$	Slight right toe-drop.	250	++	24	10	40		103.0	24	50	No paralysis.
13	8	No paralysis. Left knee jerk diminished.	850	++	48	5	15		102.5	60	20	Developed partial paralysis in arms, legs, and abdominal muscles.
14	$1\frac{7}{12}$	No paralysis.	120		31	5	20		103.0		25	Died in 66 hrs.
15	4	" "	360	++	36	10	20		103.2		30	" " 28 "
16	8	" "	730	++	6	10	20		102.0	96	30	Slight partial paralysis of both arms. Subsequent recovery complete.
17	2	" "	60	±	36	6	25		102.0	22	31	Subsequent rise to 102°F. Variable temperature for 5 days. No paralysis.
18	5	" "	379	+	$22\frac{1}{2}$	10 (2 doses).	25		103.4	32	35	No paralysis.
19	4	" "	150	++	24	10	25		102.4	15	35	" "
20	$1\frac{1}{12}$	" "	75	++	18	10	25		101.4	22	35	" "
21	$3\frac{1}{2}$	" "	230	++	66	5	40		102.4	32	45	" "
22	$3\frac{1}{2}$	" "	88		76	20	30		101.6	36	50	" "
23	5	" "	250		30	15	40		101.2	12	55	" "
24	$1\frac{1}{2}$	" "	40	+	31	25	35		103.0	16	60	" "
25	5	" "	260	+	48	22	45		103.2	22	67	" "
26	23	" "	40	++	38	20		100	101.0	48	120	" " Hyperesthesia disappeared in 48 hrs.

DISCUSSION.

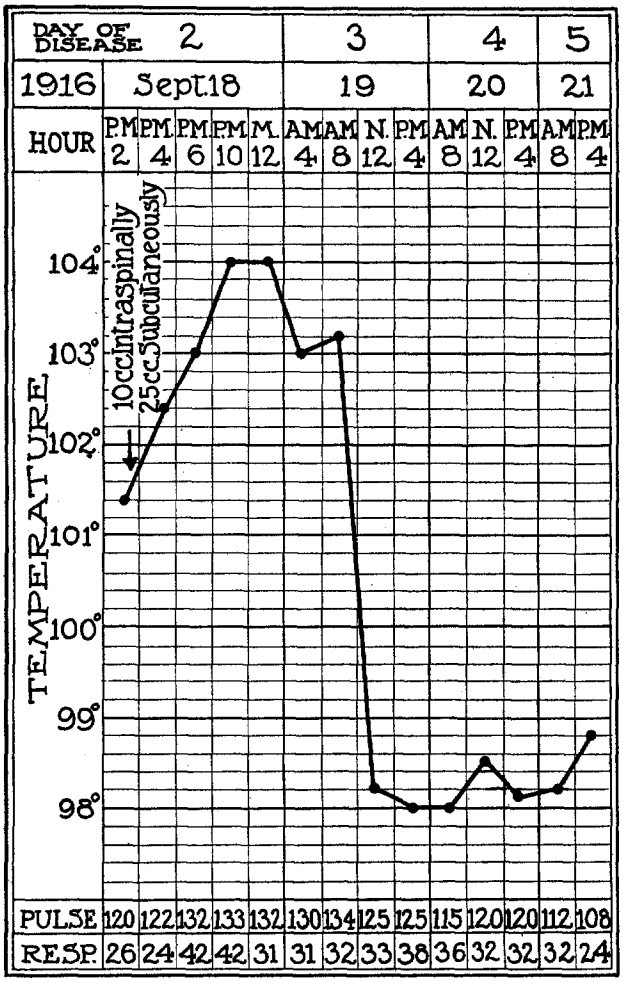
Since the data in the twelve cases which showed paralysis at the time serum was first given are less complete, and the control of the conditions was less perfect, we shall dismiss them with few comments.



TEXT-FIG. 1. Temperature chart of Case 7.

One patient died 10 hours after the serum was given, two patients suffered some degree of extension of the paralysis, while the remaining nine showed no extension of the paralysis.

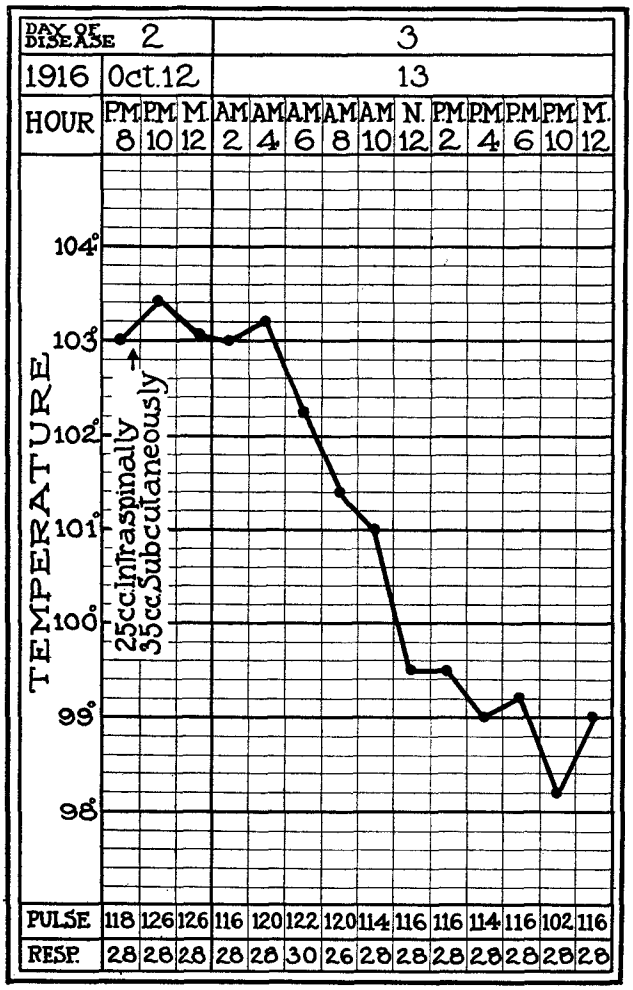
The circumstances surrounding the group of fourteen cases in which no paralysis was detected at the time serum was administered are more favorable for a conclusion. Two of the patients of this group developed respiratory paralysis and died; and two others de-



TEXT-FIG. 2. Temperature chart of Case 20.

veloped some degree of weakness or partial paralysis of certain muscle groups. The ten remaining cases (71 per cent) never showed any detectable weakness.

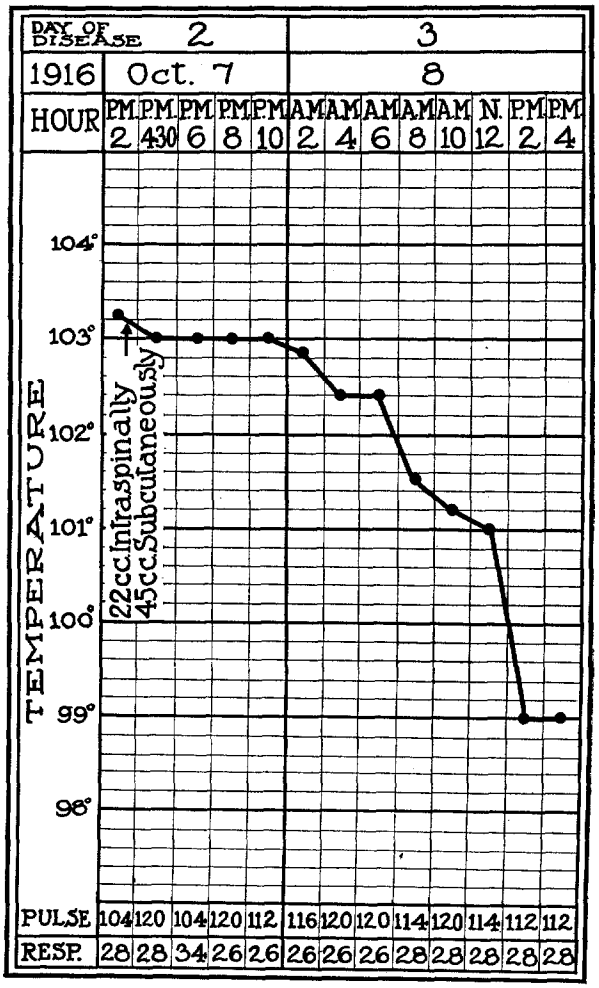
The analysis should be carried further. In the ten instances in which no paralysis occurred, the fever, sometimes high, tended to fall rapidly to normal, the average time of the fall being 25.7 hours.



TEXT-FIG. 3. Temperature chart of Case 24.

The critical fall in temperature is shown in the charts (Text-figs. 1 to 4). In this connection it is desirable to allude to two incidental effects of the intraspinal injection of an homologous serum. The

first is the following sharp rise in temperature, of brief duration; the second is the increase in stiffness of the neck and even the accentuation of the opisthotonos already present. The former has been



TEXT-FIG. 4. Temperature chart of Case 25.

frequently noted especially after the intraspinal injection of salvarsanized serum employed in the treatment of syphilis of the nervous system;[13] the latter results from the irritation or even transient asep-

[13] Ellis, A. W. M., and Swift, H. F., *J. Exp. Med.*, 1913, xviii, 428.

tic inflammation incited in the meninges by the serum. Coincident with this condition the cerebrospinal fluid may become turbid (Case 22) from emigrated leukocytes; but the inflammation lasts only a day or two and is in no way a source of danger.

In each case there was an increase in the number of cells in the fluid withdrawn by lumbar puncture as well as excess of globulin. In several instances the cell count was high (Cases 6, 13, and 16). In nine of the fourteen included in the second group, the count exceeded 100 cells per c.mm. As far as this is an index in pointing to the probable development of paralysis, it is favorable to the serum treatment.

This moderate number of cases is sufficient to demonstrate the harmlessness of the serum when introduced intraspinally under suitable conditions. The gravity method of injection was always employed. Each sample of serum was tested bacteriologically and found to be sterile; and in every instance a Wassermann test was employed to exclude syphilitic taint. Particular care was taken to obtain serum free from corpuscles or hemoglobin. Only perfectly clear and colorless samples were employed for injection. We believe that attention should be directed to these points in order that the reaction to the presence of the serum, a foreign body in the subarachnoid space, may be reduced to the minimum.

Finally, we had in mind that in acute poliomyelitis to a greater extent than in epidemic meningitis, the substance of the spinal cord and medulla suffer injury. On that account they may suffer even more readily the ill effects of increased intracranial pressure. In poliomyelitis the lumen of the blood vessels is already encroached upon by the perivascular infiltration. Hence the serum should be injected under low pressure and only after the previous withdrawal of a greater amount of spinal fluid than the serum injected. Should symptoms referable to increased intracranial pressure arise, they may be relieved by prompt withdrawal of the injected fluid. In one instance only (Case 22) in our series did we resort to the withdrawal as a precautionary measure, although the removal was not urgently demanded.

In estimating the probable effects of the serum other considerations

arise. The first relates to the period of the disease at which the serum is injected. If there is analogy between this disease and epidemic meningitis, for example, then the earlier the serum is injected, the more pronounced should be the effects. In other words, it should theoretically be easier to prevent paralysis altogether or to limit its extent and intensity than to bring about its rapid retrogression. This fact follows from the pathology of poliomyelitis[14] and from the manner in which automatic arrest of the pathologic process takes place.

The treatment was begun with definite plans for administering the serum early in the disease and in large amounts. The time limit between onset and treatment was set at 48 hours. It is obviously impossible to adhere strictly to this rule, but out of the twenty-six cases reported, eighteen were treated within this time. Apparently the best results are obtained in cases treated within 30 hours after onset, though beneficial results were obtained in one instance as late as 96 hours after onset (Table II).

The serum administered was obtained from persons recently recovered from poliomyelitis, at which period it is supposed to contain immune substances in greatest concentration. We suggest that if serum is used from patients whose attacks are more remote, correspondingly larger doses should be employed.

Recovery from poliomyelitis depends upon a process of self-immunization, and the indications are that the immunization takes place rapidly. On the 6th day of the disease, neutralizing immune bodies are already present in readily detectable quantities in the blood.[10] Therefore, what the therapeutic employment of the serum seeks to accomplish is the anticipation by artificial means of this process of autoimmunization. Probably also the artificial may have advantages over the automatic method. The latter operates chiefly by the medium of the blood, although doubtless the increased permeability of the meninges and choroid plexus in the damaged nervous organs permits an escape of immune bodies into the cerebrospinal fluid. It has been shown by direct experiment that the neutralizing immune bodies pass into the aseptically inflamed cerebrospinal fluid.[10] But

[14] Flexner and Lewis, *J. Exp. Med.*, 1910, xii, 227.

TABLE II.

Effect of Early Administration of Serum.

Case No.	Time between onset and treatment.	Result.	
	hrs.		
2	96	Marked improvement.	+*
5	96	No change.	0
22	76	" paralysis.	+
3	72	Marked improvement.	+
9	72	Increase in paralysis.	−
1	72	Died in 10 hrs.	−
21	66	No paralysis.	+
4	54	Improvement.	+
7	48	No increase in paralysis.	+
8	48	Slight " " "	−
13	48	" " " "	−
25	48	No paralysis.	+
26	38	" "	+
15	36	Died in 28 hrs.	−
17	36	No paralysis.	+
14	31	Died in 66 hrs.	−
24	31	No paralysis.	+
6	30	" "	+
23	30	" "	+
19	24	" "	+
12	24	" "	+
10	24	" "	0
18	22½	" "	+
20	18	" "	+
11	12	Improvement.	+
16	6	Slight increase in paralysis.	−

* In the tables + indicates improvement in the condition of the patient; 0 indicates no change; and − indicates that the disease was not checked.

it is generally conceded that the most direct route to the interstices of the central nervous organs is by way of the cerebrospinal fluid.[15] Hence the introduction of the immune serum intraspinally and intravenously at the same time should afford the quickest and most effective way of supplying the nervous tissues with the immunity substances which neutralize and inactivate the virus of poliomyelitis.

It has been stated, moreover, that larger amounts of serum should

[15] Flexner, S., *J. Am. Med. Assn.*, 1913, lxi, 447, 1872.

be administered in the early stages, in which the greatest benefit is expected. Table III shows that the best results are obtained in cases receiving a total of more than 30 cc. of serum.

TABLE III.

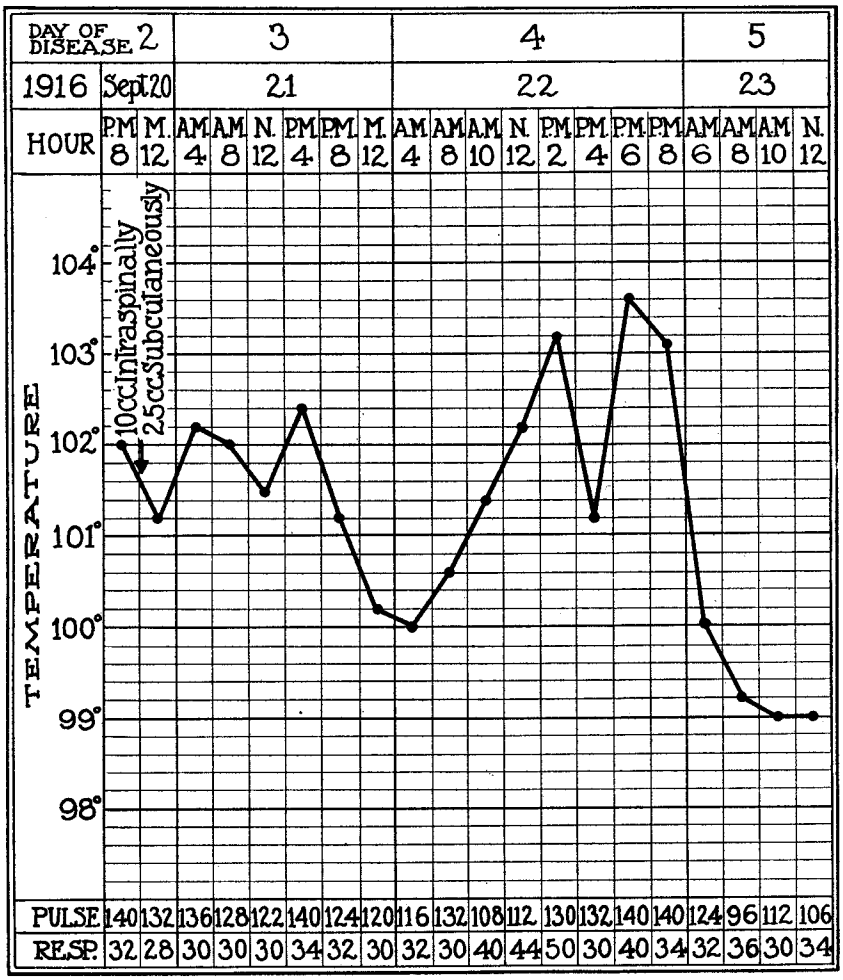
Effect of the Amount of Serum Administered.

Case No.	Total amount of serum given.	Result.	
	cc.		
10	5	No increase in weakness.	0
13	20	Slight " " paralysis.	−
8	25	" " " "	−
14	25	Died in 66 hrs.	−
1	30	" " 10 "	−
15	30	" " 28 "	−
16	30	Slight increase in paralysis.	−
17	31	No paralysis.	+
5	35	" change.	0
7	35	" increase in paralysis.	0
18	35	" paralysis.	+
19	35	" "	+
20	35	" "	+
6	35	" "	+
11	40	" "	+
21	45	" "	+
12	50	" "	+
22	50	" "	+
9	55	Definite increase in paralysis.	−*
23	55	No paralysis.	+
24	60	" "	+
25	67	" "	+
4	70	Improvement.	+
3	75	Marked improvement.	+
2	80	" "	+
26	120	No paralysis.	+

* Serum given 72 hours after onset of symptoms.

The patients who received a total of more than 30 cc. within 48 hours after the onset, without regard to the clinical condition, age, or temperature, seemed to be benefited in every case but one, and in this case the temperature quickly dropped to normal (Table IV).

It seems highly desirable, therefore, to administer at least 50 cc. of serum in every case and if possible to treat cases within 30 hours after the onset of the first symptoms.



TEXT-FIG. 5. Temperature chart of Case 6.

The plan of giving single large doses was strictly adhered to in this series, but a study of the temperature charts and clinical notes indicates that in some cases either larger doses or a second dose of serum

TABLE IV.

Results in Cases Treated within 48 Hours after Onset with More than 30 Cc. of Serum.

Case No.	Time between apparent onset and treatment.	Total amount of serum given.	Result.
	hrs.	*cc.*	
7	48	35	0
25	48	67	+
26	38	120	+
17	36	31	+
24	31	60	+
6	30	35	+
23	30	55	+
19	24	35	+
12	24	50	+
18	22½	35	+
20	18	35	+
11	12	40	+

should have been given. Case 6 received in all 35 cc. of serum and recovered rapidly without paralysis. However, the temperature chart suggests that a second dose of serum should have been given on the 4th day of the disease (Text-fig. 5).

CONCLUSIONS.

1. Serum taken from recently recovered cases of poliomyelitis may be employed in its treatment and probably yields the best results.

2. When sterile for ordinary bacteria, free of corpuscles and hemoglobin, and when injected by the gravity method, observing well known rules of caution, it may be employed without danger.

3. The serum should be injected both intraspinally and intravenously, the latter either directly or by way of the subcutaneous tissues.

4. The earlier in the course of the disease the serum is employed in suitable doses, the more promise there is of benefit.

5. The action of the serum appears to be more precise and definite in arresting paralysis than in rapidly bringing about its retrogression.

6. The decision to employ the serum should rest upon a clinical examination supported by the results of the microscopic and chemical study of the cerebrospinal fluid.

7. The question of multiple and repeated injections of the serum

has not yet been worked out. In the cases here reported and especially in the group in which no paralysis existed at the time of the first injection, the pathologic process either did not progress at all, or where there was extension, as in Cases 14 and 15, the upper segment of the spinal cord became rapidly involved, and was followed by respiratory paralysis and death. Probably in cases in which some degree of muscular weakness develops soon after the injection of serum, reinjection 12 to 24 hours later may be advantageous. The temperature curve may serve to indicate the time for reinjection.

8. The favorable results thus far achieved in human beings by means of the immune serum support and extend those obtained experimentally in monkeys and indicate, as was foreseen, that the milder or less fatal form of poliomyelitis appearing in man is even more amenable to the serum treatment than is the highly fatal disease produced by inoculation in monkeys.