

dilutions of the serum were made with salt solution, and mixed in small test tubes, as also in Wright's pipets, with equal parts of 5 per cent. suspensions in salt solution of certain washed red cells, *B* and *C*, which the undiluted serum agglutinated.

Dilutions of the plasma of the citrated blood *A* were made, similar to those of the serum, but the proportion of red cells was kept the same as in the original citrated blood. For this the citrated blood was distributed in a number of graduated tubes, centrifugalized rapidly, the supernatant fluid measured and diluted appropriately, and, when the red cells had been suspended and centrifugalized, all of the fluid was pipetted away except the original volume, and the cells were resuspended. The diluent used was sodium citrate in salt solution (1 part 10 per cent. sodium citrate to 9 parts 0.95 sodium chlorid). Nine parts of each of the combinations thus obtained were mixed in Wright pipets with one part of the whole citrated bloods *B* and *C*. The microscopic findings after fifteen minutes were compared with those in the serum mixtures after one and two hours. They gave identical results. Agglutination occurred when dilutions of serum or plasma up to 1 part to 7 of the diluent had been used for the mixtures, but not when 1 part to 15 had been employed. It was slight with 1:7 plasma and no better marked with 1:7 serum.

The experiment shows that a weak agglutinin may be demonstrated quite as well with mixtures of citrated whole bloods as with serum and a diluted suspension of washed red cells in salt solution. The interference of neutral red cells does not constitute a difficulty.

CONCLUSION

The test here described compares well in delicacy with those already in use, but we wish to insist only on its practicability. It enables one to determine within a few minutes, so far as agglutination and hemolysis are concerned, whether or not the blood of a donor is suitable for transfusion.

INTRASPINAL ADMINISTRATION OF ANTITOXIN IN TETANUS

NOTES ON A SERIES OF CASES*

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As the result of a series of animal experiments conducted at the Research Laboratory of the Department of Health by Dr. William H. Park and myself¹ in order to determine the curative value of the intraspinal administration of tetanus antitoxin, and by which the superiority of this method was conclusively shown, every effort has been made during the past year to get into immediate touch with physicians and hospitals in and about the city of New York having cases of tetanus under their care, and induce them to give antitoxin as soon as possible by the following method:

1. From 3,000 to 5,000 units into the lumbar region of the spinal canal, preferably under an anesthetic, the volume of fluid injected being brought up to 10 or 15 c.c. by the addition of sterile normal saline, the exact amount being regulated according to the age of the patient and the amount of spinal fluid withdrawn.
2. Ten thousand units intravenously at the same time.

3. Repetition of the intraspinal dose in twenty-four hours.

4. A subcutaneous dose of 10,000 units three or four days later.

The well-recognized adjuvants to specific treatment—quiet, subdued light, sedatives, etc.—were, of course, understood as a necessary part of the therapeutic measures.

In no case has the physician objected to giving an intraspinal injection of antitoxin when so advised. Some, however, have given it in much greater quantities and by other methods in addition to that recommended, usually before I was able to consult with them.

Reports of twenty cases have thus been collected, in all probability representing a majority recognized as tetanus during this period in and about the city of New York. I have seen about half of the patients personally, in consultation. In others, the physicians have been kept in constant touch by telephone or through a clinical assistant during the progress of the case. In four cases, the histories have been furnished by the physician on request, the treatment given being exactly that recommended by the published article referred to above. In all cases the antitoxin used was furnished by the Department of Health.

A brief abstract of the clinical histories follows:

CASE 1.—F. D., girl, aged 10 years, seen in consultation with Drs. W. B. Anderton and A. A. Smith, fell, striking her forehead on the ground, receiving a lacerated wound three-quarters inch long over one brow. This was properly disinfected and sutured, healing promptly. Seven days later there was a facial paralysis on the side on which the wound was received. Thirty-six hours later, the jaws were firmly locked. Eight hours after this symptom was noted, the patient received 3,000 units of antitoxin intraspinally and 10,000 intravenously. Several subcutaneous injections were later given. The tetanic spasms were largely confined to the muscles of the jaw and pharynx, and later, the abdominal muscles; attempts at swallowing and the slightest external irritation caused contractions of the muscles of the throat and larynx, cyanosis, general convulsions and unconsciousness. Such convulsions occurred on fifty or more occasions, together with innumerable minor spasms. Pneumonia developed later, resolution being very long delayed. After a protracted convalescence and extreme emaciation, the patient made a perfect recovery.

CASE 2.—Thomas B., laborer, was admitted April 1, 1914, to the New York Hospital, with multiple lacerations of scalp and traumatic amputation of toes of the right foot. The wounds were immediately disinfected with iodine and irrigated with iodine solution. The following day, amputation of the toes was performed. April 10 (incubation nine days), there was slight stiffness of the jaws, which was not reported until the following morning. April 11, 1,500 units of antitoxin were given in the tissues about the wound and 3,500 intravenously, later on the same day, 3,000 units into the tissues about the wound and the same amount intravenously. April 12, the patient was very much worse, and was given 13,000 units intravenously, 8,000 intraneurally and 7,000 into the tissues about the wound. April 13, I was first consulted and the patient visited. His condition was still more unfavorable. There was marked opisthotonos. Eight thousand units of antitoxin were given into the spinal canal and 9,000 intravenously. Following the intraspinal injection the temperature rose to 105; there were severe headache, convulsions and semicoma. April 14, the patient was comatose throughout the day. April 15, the patient was conscious, and there was less rigidity. April 16, there was much less rigidity; the patient swallowed fairly well for the first time. The patient continued to improve and was discharged cured, April 30.

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¹ Read at the Meeting of the Association of American Physicians, Washington, D. C., May 11, 1915.

1. Park, W. H., and Nicoll, Matthias, Jr.: Experiments on the Curative Value of the Intraspinal Administration of Tetanus Antitoxin, *THE JOURNAL A. M. A.*, July 18, 1914, p. 235.

Comment.—Through a series of misunderstandings, this patient received still further intravenous injections of antitoxin following the intraspinal dosage, although an examination of his blood showed a tremendous antitoxic content. How much credit should be given the single intraspinal dose for the recovery in this case it is difficult to say. It is to be noted, however, that the first real improvement followed shortly after its administration.

CASE 3.—Gustav H., aged 23, carpenter, admitted to St. Vincent's Hospital, June 27, 1914, had injured the tips of his fingers in some way, June 16. A definite history could not be obtained. Three days before this, the patient had a pustule on his neck, which was opened on the 20th. There was no other history of injury. June 21 (incubation five or eight days), he first noticed that his jaw was stiff; two days later, this was much more marked and had spread to the neck, back, arms and legs. On admission, there was marked opisthotonos, and the jaws were tightly locked. The slightest disturbance caused a convulsion. The patient's body rested on the heels and back of the head. The abdomen was boardlike. Treatment on the first day after admission consisted of 5,000 units of antitoxin intraspinally and 5,000 intravenously; June 28, 5,000 subcutaneously. The opisthotonos continued. July 1, 5,000 units were administered intraspinally, five hours after which the patient became delirious with a rise in temperature to 105. From July 4 to July 8, the rigidity decreased daily. July 18, the patient was discharged, cured.

CASE 4.—Boy, said to have been vaccinated sixteen days previously, the vaccination wound having apparently become infected one week after vaccination, developed a slight stiffness of the jaw. Four days after the onset of this stiffness, he was admitted to the Roosevelt Hospital, where it was noted that the legs were very stiff, the arms less markedly so. There was slight trismus. He was given, on admission, 2,500 units intraspinally, 5,000 units intravenously and 1,500 units intramuscularly and in the tissues about the wound. The latter two injections were repeated the next day. On the third and fifth day he received intraspinal injections. Improvement in symptoms began about the third day and continued until discharge thirteen days after admission, when patient was well.

Comment.—This case, though comparatively mild, was unquestionably one of tetanus. Many of the injections given could well have been dispensed with.

CASE 5.—G. T., boy, aged 10 years, was admitted to New York Hospital, Oct. 9, 1914. October 2, he ran a rusty nail into the sole of the left foot. October 9 (incubation seven days), there was stiffness of jaws, and some antitoxin (dose not known) was given intramuscularly. On admission, the teeth could not be separated and there was some tension in the calf of the left leg. All reflexes increased. Eight hours after admission, 3,000 units of tetanus antitoxin were given intraspinally and 1,500 about the wound, which had been opened. A few hours later, 1,000 were given intravenously. During the night, there were minor convulsions, accompanied by piercing screams every fifteen minutes. On the 12th, there were some dysphasia, abdominal rigidity and stiffness of the neck. The teeth were separated one-half inch. Intravenous injection of 9,000 units was made; there were general convulsions. October 11, there were convulsions lasting ten minutes, opisthotonos and a great deal of pain. October 12, there were convulsions for twelve minutes, stertorous breathing, cyanosis and great rigidity for half an hour following. October 13, the boy was comfortable and swallowed well. Intraspinal injection was made of 5,000 units. From October 14, there was a gradual improvement. The patient was discharged, cured, October 24.

CASE 6.—M. B., boy, aged 8 years; was admitted to Bellevue Hospital June 17, 1914. The history of injury due to a fall six days previously and the presence of an old ulcer on the right shin did not serve to establish the incubation of the disease. Five days before admission his jaw began to be stiff. This stiffness extended to other muscles day by day. On admission he was absolutely rigid from his neck to his feet. His teeth could be separated but one-fourth inch. June

18, under an anesthetic, he was given 5,000 units of antitoxin intraspinally and 5,000 subcutaneously. The mind was perfectly clear; the arms alone could be moved freely. There were incontinence of urine and feces. The boy was fed by gavage. June 25, he was very much improved. He bent at the waist when lifted. The mouth opened five-eighths inch. June 28, he moved the legs and arms freely; the spine was no longer stiff; the mouth opened widely; he ate well.

Comment.—This child was in a desperate condition at the time of giving antitoxin. On theoretical grounds we should not expect that antitoxin would be of much avail, when given at so late a period of the disease, and yet the improvement followed so soon after its administration that it would seem that antitoxin should be given the credit for it.

CASE 7.—R. M., boy, was admitted to the Hospital of the Holy Family, April 15, 1914, having run a nail in the sole of his foot at some time previously not possible to determine. There was apparently locking of the jaws three days before admission, at which time the muscles of the neck and back were rigid. The wound on the sole of the foot was opened and dressed. April 16, 5,000 units of antitoxin were given intraspinally, 10,000 intravenously and 3,000 intramuscularly. The child's condition gradually improved, and he was discharged cured about two weeks after admission.

CASE 8.—D. R., boy, aged 10 years, a patient of Dr. Ramsdell of White Plains, complained, Sept. 14, 1914, of pain in the back and slight stiffness of the jaw and of left arm. This child was vaccinated August 17. August 31, the vaccination wound not having been dressed for nine days, was in an unfavorable condition, there being considerable pus at the site of vaccination and swelling of the arm. A shield was later applied, on the mother's initiative. There was a further history of injury to the wound on several occasions. The incubation of the disease could not, therefore, be determined. The symptoms of tetanus increased until September 18, when the patient was given an intraspinal injection of 5,000 units of antitoxin and 45,000 units (through a misunderstanding) intravenously. Following this, there was a marked exaggeration of all the symptoms; a rise of temperature and opisthotonos, lasting about forty-eight hours. The patient gradually improved and was discharged cured in two weeks.

CASE 9.—Boy, aged 6 years, a patient of Dr. Joseph Wheelwright, gave a history of trauma nine days before the locking of the jaws. Forty-eight hours later an intraspinal injection of 5,000 units and intravenous injection of 10,000 units of antitoxin were given. Subsequently this was repeated. The case was a very severe one with many convulsions, and the patient recovered fully in the fourth week.

CASE 10.—A., male, at St. Vincent's Hospital, following a traumatic amputation of finger fourteen days previously, developed severe spasms of the abdominal muscles; later his jaw became locked and the rigidity was general; there were a number of convulsions. Thirty-six hours after the development of symptoms, 5,000 units of antitoxin were given intraspinally and 10,000 intravenously. There was marked anaphylaxis immediately following the injection, with urticaria covering the entire body and suggestion of edema of the glottis and lungs. This passed away shortly after the administration of a large dose of epinephrin. The intraspinal dose was repeated forty-eight hours afterward, as the patient had grown worse and had had a number of convulsions. The serum reaction following this was not so severe as in the first instance. Improvement in symptoms began to show in two or three days, the patient making a perfect recovery from his tetanus, but developed mental symptoms consisting of intermittent attacks of acute mania and delusions of persecution. After a number of weeks this completely disappeared and his condition was normal.

CASE 11.—T. D., woman, aged 30 years, was seen by Drs. William H. Ross and H. E. Chauvin of Brentwood, N. Y., September 30, 1914. She had given birth to a child two weeks previously in very dirty surroundings. The symptoms of tetanus were very marked, and many convulsions continued for five days. Two days after the onset of symptoms, 10,000 units of antitoxin were given intraspinally and 5,000 intravenously; the later dose was repeated three times in

three successive days. The patient was discharged cured except for a slight trismus which lasted for three days longer, October 11.

CASE 12.—R. W., boy, aged 11 years, was seen by the physicians mentioned above, Sept. 6, 1914. There was a wound over one patella, received eleven days previously. Five thousand units of antitoxin were given intraspinally and 5,000 intravenously on the day following the development of symptoms. The intravenous dose was repeated. Eight convulsions occurred during the first three days, the temperature running high during this time. The patient was discharged cured eight days after admission.

CASE 13.—W. M., man, aged 20, seen by the same physicians Jan. 3, 1915, had received a punctured wound of the instep three weeks previously. There was complete trismus and stiffness of the whole body. Ten thousand units of antitoxin were given intraspinally and 5,000 intravenously the day after the symptoms were noted. The intravenous injection was repeated the next day. The patient was discharged cured in two weeks.

CASE 14.—M. G., woman, aged 22, gave no history of traumatism. Four days before admission to the Lebanon Hospital, there was slight rigidity of the neck and difficulty in opening the mouth. The next day the jaws were completely locked. On the day before admission she had general convulsions. On the day following admission, five days after the onset of symptoms, she was given 5,000 units of antitoxin intravenously and 750 units intraspinally. On the second and third days she was given 5,000 units intraspinally under an anesthetic. The patient also received injections of magnesium sulphate (25 per cent.) subcutaneously and intramuscularly three times a day in doses of 30 c.c. for seventeen days, without apparent relaxing effect. The course of the disease was rather protracted with many convulsions. The patient was discharged cured seven weeks after admission.

CASE 15.—L. M., male, aged 18 years, was admitted to St. Peter's Hospital, March 27, 1915, with a crushed and lacerated wound of the great toe. The wound was immediately disinfected and properly dressed. March 30, the tip of the toe sloughed off. April 6, the patient had a severe chill and complained of sore throat. There was noted a slight stiffness of the jaw. In the afternoon there were marked stiffness of the back, and occasional slight convulsions when the patient was disturbed. Twenty thousand units of tetanus antitoxin were given intraspinally four hours after the occurrence of the chill. On the 7th, the symptoms increased in severity, convulsions occurring on the slightest irritation. There were marked opisthotonos and rigidity. Ten thousand units of antitoxin were given intraspinally under an anesthetic. On the 8th, the patient's condition was about the same. Ten thousand units of antitoxin were given intravenously. After the tenth day, the convulsions stopped; the rigidity continued some time longer. April 22, the patient was up and about with slight rigidity. He was discharged cured a few days later.

CASE 16.—M. S., man, aged 24, admitted to Bellevue Hospital Feb. 4, 1915, with very indefinite history, was said to have run a splinter into his foot three weeks previously. Two days before admission he complained of great pain in his back and neck, which was stiff; later he could not open his mouth. On examination the day after admission, it was found that his jaw was markedly locked, the abdominal muscles of a boardlike rigidity, and the back slightly arched. He was given 5,000 units of antitoxin in the spinal canal and 10,000 in the vein. The intraspinal dose was repeated two days later. The symptoms increased in severity for a day or two, frequent tonic spasms causing the patient to cry out with pain. After a few days all symptoms began to ameliorate, and he was completely well in about two weeks.

FATAL CASES

CASE 17.—O. R., man, aged 34, was admitted to Bellevue Hospital, Nov. 5, 1914, for a lacerated wound of the sole of the foot, which, although treated, became infected with a foul-smelling, purulent discharge. November 12, seven days later, the patient complained of difficulty in swallowing, and

the jaws were stiff. He received 1,500 units of antitoxin intramuscularly, and twenty-four hours later, 10,000 units intraspinally and 10,000 intravenously. November 14, the temperature was lower, the jaws less stiff and the general condition improved, when the patient became markedly cyanotic, went into a condition of status epilepticus and died in twenty minutes. No necropsy was held. The exact reason for the sudden death of this patient, when the course of the disease had apparently been arrested, is by no means easy of explanation.

CASE 18.—J. O., man, aged 32, admitted to St. Peter's Hospital, Nov. 13, 1914, had stepped on a rusty nail, November 1. Seven days later, his jaw became stiff. This stiffness increased until the time of admission, when his teeth could hardly be separated. The muscles of the back and neck were stiff. November 13, five days after the onset of symptoms, he received 6,000 units of antitoxin intraspinally and 5,000 intramuscularly, the next day, 5,000 intramuscularly and 5,000 intravenously, and on the following day, 5,000 units intravenously and 7,000 intramuscularly. The patient had tonic and clonic convulsions in great numbers throughout the course of his illness. On the day before his death, the tonicity of the neck, jaws and abdomen had greatly diminished. He died following a convulsion, November 17. The short incubation in this case and long delay before beginning treatment are sufficient reasons for the failure of the antitoxin to save this patient's life.

CASE 19.—E. C., boy, aged 13 years, admitted to Bellevue Hospital, June 30, 1914, fourteen days previously had fallen and cut his head. Eleven days later he had abdominal pains and vomiting, which were regarded as due to appendicitis. On admission to the hospital he had marked opisthotonos, locked jaws and inability to swallow. A convulsion occurred on the slightest disturbance. He received 10,000 units of antitoxin intraspinally and 10,000 units intramuscularly. The patient's condition grew worse from the time of his admission and he died within twenty-four hours. The disease had evidently progressed too far to be influenced by antitoxin.

CASE 20.—W. R., physician, aged 53, was admitted to the French Hospital for herniotomy, which was performed, April 25. May 3, the patient complained that his neck felt stiff; May 4, this symptom was more pronounced and there was some rigidity of the jaw. Toward evening he could not open his mouth fully. He was given about 9,000 units of antitoxin intramuscularly. May 5, he had a general convulsion and became quite cyanotic; this was repeated twice, convulsions lasting about ten minutes. Five thousand units of antitoxin were given intraspinally and 15,000 intravenously. May 6, the patient had four convulsions, one lasting fifteen minutes. Five thousand units of antitoxin were given intraspinally. May 7, there were no further convulsions. The patient was able to take fluids by mouth, and there was much less rigidity. At 8 o'clock in the evening he had a sudden attack of pulmonary edema and rise of temperature. Later there were signs of acute cardiac dilatation. He died on the morning of May 8. This patient was very stout, and had chronic bronchitis and recurring attacks of asthma.

In judging the effect of antitoxin given intraspinally in this series of cases, it must be remembered that the patients were not selected, but that every case of tetanus reported was given the benefit of the treatment regardless of the clinical condition. The series, therefore, may be said to be fairly representative of the type of the disease occurring in and about the city of New York. A few of these patients would undoubtedly have recovered if the intraspinal injection of antitoxin had not been given or, indeed, without any treatment other than symptomatic. The results obtained, however, in the saving of life are so much more favorable than those in previous years, when large doses of antitoxin were recommended to be given by the intravenous and subcutaneous methods, that there can be no reasonable doubt that the low death rate, 20 per cent., here obtained was largely due to intraspinal dosage.