THE USE OF VACCINE-SERUM IN THE TREATMENT OF VARIOLA.

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FROM

THE MEDICAL NEWS,

June 29, 1895.

[Reprinted from THE MEDICAL NEWS, June 29, 1895.]

THE USE OF VACCINE-SERUM IN THE TREATMENT OF VARIOLA.[1]

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DURING the past few months it has been my good fortune to employ vaccine-serum in the treatment of variola, and, believing the Section of State Medicine of the American Medical Association to be the proper place for the discussion of new methods in the prevention of disease, I desire to present an epitome of the results obtained. The possibilities of serum-therapy in the management of diphtheria appear to have been fairly well established; still a few unfortunate instances occur which tend at times to shake our firm belief in its efficacy. The place of serum-therapy in syphilis, in tuberculosis, in tetanus, and in variola has not yet been fully established, and of these the last to become established will be that of variola serum-therapy; this is because cases do not occur in the practice of all physicians, and then, again, the great majority of physicians would decline to employ a means of treatment as yet in a purely experimental stage, and one that would bring them into such close contact with those patients. The bacilli of diphtheria, of

[1] Read before the Section of State Medicine of the American Medical Association at Baltimore, Md., May 7–10, 1895.

tuberculosis, of tetanus, and of cholera, having been isolated and cultivated, bacteriologists have been enabled to proceed on very proper lines; in variola, however, this is not the case, as the *specific* germ of the disease has not yet been discovered.

Dr. George M. Sternberg, Surgeon-General of the United States Army, in a paper read before the Association of American Physicians at its meeting in Washington, D. C., on May 24, 1892, entitled "Practical Results of Bacteriological Researches,"[1] presented the results of his experiments, which very clearly indicated that the blood-serum of an immune calf contains something that neutralizes the specific virulence of vaccine-virus, either bovine or human lymph, and expressed his intention to follow up this line of investigation and to test the question of its possible specific action in neutralizing the smallpox-virus in infected individuals, either before or after the development of the disease.

From the advance-sheets of a forthcoming publication[2] of General Sternberg I make the following extract: "Later I made a number of experiments upon unvaccinated children in two orphan-asylums in Brooklyn, with a view to ascertain whether blood-serum from an immune calf or from an individual who had recently suffered an attack of smallpox, if injected into the subcutaneous tissues at the time of vaccination, would prevent the development of a characteristie vaccine-vesicle. In these

[1] American Journal of the Medical Sciences, July, 1892, vol. civ, page 1.

[2] Immunity, Protective Inoculations in Infectious Diseases, and Serum-therapy.

experiments from 1 to 5 c.cm. of the serum supposed to contain an antitoxin of smallpox were injected near the point of vaccination, or, in some instances, into the other arm. The result was negative, even when serum was used from an individual who was just convalescent from a severe attack of smallpox. But it may be that a different result would have been obtained if a larger quantity of blood-serum had been used, or if it had been injected into the circulation instead of into the subcutaneous tissues."

Kramer and Boyce[1] and Landmann[2] have conducted experiments that show that the development of the vaccine-vesicle is not prevented by the use of small quantities of the blood-serum of an immune calf. Landmann[3] also shows that blood-serum from an individual who had suffered from a recent attack of smallpox exerted no noticeable influence upon the development of a case of confluent smallpox in a child five years of age when using a 25 c.cm. dose of the serum.

Sternberg[4] further thinks the blood-serum could be injected into the circulation of a smallpox patient through the median vein, and apprehends no danger from the introduction of a considerable quantity in this way.

Auché[5] has in two cases employed blood-serum obtained from a patient who had recently recov-

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[1] British Medical Journal, 1893. London. (Sternberg.)
[2] Zeitschr. für Hygiene, 1884, Bd. xviii, p. 318. (Sternberg.)
[3] Ibid. [4] Op. cit.
[5] Arch. Clin. de Bordeaux, 1893, vol. ii, p. 317—Auché: "Essai de Sérothérapie dans la Variole."

ered from variola; the quantities used were 6 and 9 c.cm. In one case the effect of the introduction of the serum was attended with a good result, but in the other case no appreciable benefit was produced.

At the request of Dr. J. J. Kinyoun, U.S.M.H.S., during my recent connection with the Smallpox Hospital of this city, I employed a quantity of vaccine-serum in the treatment of five cases of smallpox. In four cases recovery followed; in one case the disease was of such a malignant type that little hope of recovery could be entertained from any course of treatment. Dr. Kinyoun had been waiting for an opportunity to test the effects of such a line of treatment, and accordingly prepared the serum for me. His method of preparing this serum was as follows:[1] "Accordingly, on December 23, 1894, I took a liter of blood from a heifer calf which had been previously vaccinated on November 26th. At the time of bleeding the local effects of the vaccination had disappeared; the animal to all appearances was sound and well. As soon as the blood was withdrawn it was taken to the laboratory, where on the next day about 350 c.cm. of tolerably clear serum were drawn off. A part of the serum was transferred to a small sterilized flask, while another of equal quantity was passed through a special filter in order to remove the blood-corpuscles and any chance bacteria present. About 35 minims of pure vaccine-lymph (two days old) were added to 2 c.cm. of the filtered and unfiltered serum, respectively.

[1] Abstr. San. Repts., M. H.S., Wash., D.C., 1895, vol. x, p. 31. Kinyoun: "Preliminary Report on the Treatment of Variola by its Antitoxin."

After a few hours' exposure the serum was sent out to the vaccine-farm and a small heifer was inoculated in the usual manner with each sample. The results were negative in both instances, demonstrating that the process of filtration does not affect its power."

Three separate supplies of the serum were furnished me, each one at my suggestion having an increased strength; that is to say, the first supply was obtained from a calf four weeks after its recovery the second three weeks after recovery, the third two weeks after recovery. The amount to be injected, as suggested by Dr. Kinyoun, was 15 c.cm., to be repeated in about six hours should no reaction occur; this amount I increased as circumstances appeared to indicate until 30 c.cm. were given at a single dose.

The syringe used in the injection of the serum was made by Collin, of Paris, and is four inches long in the barrel and has a capacity of 20 c.cm.; there is a piece of rubber tubing four inches long adjusted to the nozzle of the syringe, into which fits the needle, an ordinary hypodermic needle, one-and-a-quarter inches long. The intervention of the piece of tubing allows more freedom of movement to the operator and prevents the possibility of the breakage of the needle by a chance movement of the patient. This piston is graduated as in the hypodermic syringe usually employed.

Preparation of the patient. There is no special preparation of the patient necessary to the employment of the vaccine-serum. It is sufficient that the surface chosen be rendered as clean as possible. This is done by first washing the surface with soap and

warm water, then with alcohol, and finally with a solution of mercuric chlorid of a strength of 1 to 3000 or thereabouts.

The point selected for the insertion of the serum does not matter materially. The usual sites have been under the right mamma, in the buttocks, and on the front of the thighs. The needle must not be driven deeply into the muscles, but into the subcutaneous tissues. I have always thrown the serum in slowly and gently stroked the surface, so that none shall be lost.

Observations at the time of injection. At the time of injection and even before its completion the surrounding tissues become edematous, hard, and pitted upon the top, as in a vaccination cicatrix; this edema covers a space from one-and-a-half to three inches in diameter; the edges are hard and the whole edematous surface becomes icy cold; this condition wears away in a few hours, leaving a small amount of soreness about the point of injection. There is no actual pain attending the injection, but patients occasionally appear faint and complain of some difficulty of breathing; these inconveniences are no doubt the result of nervousness on the part of the patient. Abscess at the point of injection has never formed in my cases.

The quantity of serum used in the cases to which I have applied this treatment has varied from 15 c.cm. to 30 c.cm. at each treatment, and from 60 c.cm. to 165 c.cm. during the entire course of the case.

The time to employ the serum is, I think, before the papules become vesicles or pustules—in other words, before the disease has time to assert itself strongly. As a prophylactic measure it could be used instead of the customary vaccination when persons have been directly exposed to the smallpox-infection. Whether I am correct or not in this last matter remains for future observers to determine. I do not

think in cases in which the disease has reached the pustular stage the employment of vaccine-serum will have any modifying effects.

Stability of the preparation. Judging from an ocular examination, I think vaccine-serum is a stable preparation, as some I have kept since the last days of December (1894) does not show any change, further than a slight precipitation, the precipitated matter disappearing when the flask is agitated.

Effects of the treatment. Under this treatment the pulse increases in volume and in number of pulsations; the quantity of albumin in the urine decreases; there is a rise of temperature followed by a fall; the papules abort and the pustules desiccate, and there is very little pitting. While employing the serum other treatment is given. In five cases in which the vaccine serum was used one patient was in a septic state when the treatment was commenced and died of malignant variola; the other four were cured of variola; one, however, after being cured of confluent variola and discharged from the hospital, was readmitted with what I supposed to be a genuine case of cowpox, a septic infection or an unfortunate sequela of the serum. She did not have a second attack of variola vera.

Case I.—W. G., male, colored, aged twenty-eight years, a laborer, was admitted to the Small-pox Hospital December 21, 1894, ill with *variola maligna*. He had been successfully vaccinated four years ago. His condition on admission was very unfavorable, the eruption was confluent, accompanied with a high temperature and violent delirium. The temperature from December 21st to 28th varied from 103.6° to 99°. During this time the temperature steadily declined, whereas the pulse and respiration remained high, the delirium continuing about the same. This was so violent at times that restraint became necessary. On Decem-

ber 25th considerable hemorrhage occurred in the pustules, and there was much gastric irritation. On December 28th, at 10 A.M., the patient's condition was as follows: Temperature 99°, pulse-rate 120, respirations 32 and quite superficial. The patient was conscious at times, but very weak. A small quantity of urine was passed, and it was found to contain albumin 10 per cent. per volume.

At this time 15 c.cm. of the serum were injected subcutaneously after the skin had been carefully disinfected. At 11 A.M. the respiration became deeper, the pulse stronger and fuller, the temperature 99.6° The man was very thirsty. The edema caused by the injection had entirely disappeared. At 2.30 P.M. another dose of 15 c.cm. was given, his condition being about the same, the temperature 100°, the pulse 130, the respirations 32. The respiration was deeper, the pulse stronger, and there was considerable expectoration. At 9 P.M. another dose of 15 c.cm. was given. At the time of the injection the skin over the face had become very dry, hard, and bleached, the skin in its texture resembling very much the appearance of elephant-hide. The temperature was now 99°, the pulse 120, respirations 28 and shallow; expectoration was free, and tinged with blood.

On the morning of the 29th another dose of 15 c. cm. of serum was given, the temperature being 98°, the pulse-rate 120, the respirations 32. No urine had been passed during the preceding twelve hours. The man was plainly growing weaker, and he died on the morning of the 31st. No post-mortem examination was held. The total quantity of serum injected was 60 c.cm., the number of injections four. No effect was produced upon the eruption or upon the disease. The peculiar feeling of the skin in this patient is frequently noticed in malignant cases.

CASE II.—B. L., a male, colored, aged twenty

years, a driver, was admitted to the Smallpox Hospital on January 4, 1895, with the diagnosis of variola. He had been successfully vaccinated some time before. An eruption lasting about five days extended over the face, chest, arms, body, and legs. Upon his admission his axillary temperature was 99.8°, the pulse-rate 98, respirations 24. He had considerable bronchitis. At 11 A.M., January 5th, after thorough disinfection of the part, 15 c.cm. of the serum were subcutaneously injected at a point about 1½ inches below the nipple. As the serum was injected quite a large wheal, two inches square, appeared, very tightly stretching the skin, and having at its middle numerous pits, appearing like a vaccination-cicatrix, and covering a space of about one inch square. As the wheal was masséed the pits disappeared. During the process of injection the patient became very much frightened, but experienced little if any pain. The urine on examination showed 8 per cent. of albumin per volume. One hour after the injection the temperature registered 100.8°, the pulse 88, strong, the respirations 24 and deeper. At 5 P.M. of the same day 15 c.cm. of the serum were injected. Temperature was then 102,° the pulse-rate 90, full and strong, the respiration deep and full, the man expectorating freely. At 6 P.M. the temperature was 100.8°, the pulse-rate 96, the respirations 30. On January 6th the temperature was 102.2°, the pulse 92, full and strong, respirations 24 and of good depth. The patient complained of soreness at the point of injection.

Quite a notable change occurred in the pustules, which appeared to be losing their moist character, having an inspissated appearance, and quite a number of very small new pustules appeared in the healthy skin. At 8 P.M. the man was in a profuse perspiration, the temperature was 99.4°, the pulse 88, and respirations 28 ; the urine showed a marked

decrease in the quantity of albumin. Thirty c.cm. of the serum were again administered. About one-half an hour after this injection the patient complained of a difficulty in breathing, but this passed off in the course of an hour. At 9 P.M. another dose of 30 c.cm. was given. This produced no ill effects. The temperature was 102°, the pulse-rate 100, the respirations 26. Albumin was present, but in smaller quantity. On the following day there was a marked change in the eruption. All the former pustules were now drying, and the smaller ones that had appeared the previous day seemed to have aborted. The general condition of the patient was more favorable. No further serum-treatment was given, and the man was convalescent on January 16th. During a period of forty-eight hours 105 c.cm. of the serum were given in five injections.

On January 16th the scabs were becoming detached from the skin, and presented a very favorable appearance. There were no indications that there would be any pitting, whereas two other cases, not receiving the serum, to all appearances identical with this one, will be badly marked.

CASE III.—B. S., a male, colored, aged nineteen years, a waiter, who had never been vaccinated, was admitted to the Smallpox Hospital with the diagnosis of variola. On January 25, 1895, at 8 P.M., he had an eruption on the face, chest, and scalp; he also suffered from pharyngitis, and had a temperature of 103°. On the 26th, at 10.30 A.M., his temperature was 100.5°, the pulse-rate 88, the respiration 28; 23 c.cm. of serum (second supply) were injected into the right side of chest. The usual wheal of edematous tissue followed. At 3 P.M. the temperature was 102.4°. At 7 P.M. the temperature was 102.6°, the pulse-rate 96, the respirations 24. Injections of 22 c.cm. were made. On the 27th the morning temperature was 100°, the pulse 98,

the respirations 26. No further serum treatment was given, as the papules were aborting. On February 2d the man was convalescent. The number of injections was 2, and the quantity of serum used was 45 c.cm.

CASE IV.—F. H., a male, colored, aged nineteen years, a laborer, was admitted to the Smallpox Hospital on the night of January 18, 1895, with the diagnosis of variola. He had been vaccinated successfully some years ago. As this man was in a very filthy condition he was given a hot (bichlorid) bath upon his admission, when the points of eruption showed themselves very prominently and profusely, giving indications of a severe attack of the disease. The temperature was 99.8°, the pulse 88 and strong, the respirations 24.

On January 19th, at 11 A.M., his temperature was 100.2°, the pulse 84, the respirations 22. There were papules on his face, the urine was amber in color, its reaction neutral, its specific gravity 1012, and there was no reaction of albumin to heat and nitric acid. An injection of 15 c.cm. of the serum was made into the right buttock, followed by the usual appearances, but in addition the edematous surface became very cold. There was no pain. At 11.30 A.M. his temperature was 99 8°, his pulse 84, and the respirations 24 and fuller. At 2 P.M. the temperature was 100.2°, the pulse 100, the respirations 30. We now injected 30 c.cm. of serum into the left buttock, with the same results as before. At 3 P.M. the temperature was 100°, the pulse 96, the respirations 28. At 8 P.M. the temperature was 101.8°, the pulse 108, the respirations 28. We again injected 30 c.cm under the right nipple. This caused some burning and uneasiness, and again appeared the edema and coldness as before noted. There was no change in the eruption. At 10 P.M. the temperature was 101.8°, the pulse 112, the respirations 30.

There was no albumin in the urine. On January 20th, at 11 A.M., the temperature was 100.2°, the pulse 102, the respirations 24. We again injected 30 c.cm. into the left buttock. The point of the insertion of the needle in the chest-wall was still sore, but that of the buttock was not noticeable. At 3 P.M. the temperature was 101.8°, the pulse 114, the respirations 34. The man complained of considerable chest-oppression. At 7 P.M. the temperature was 101.8°, the pulse 110, the respirations 24, and he had no further oppression. On January 21st, at 10.30 A.M., the temperature was 99.4°, the pulse 88, the respirations 28. The eruption had become dry, and only three new spots had appeared, one small one on the right side of the neck and two small ones on the left side. We now injected 30 c.cm. into the front of the thigh. At 3 P.M. the temperature was 99.8°, the pulse 96, the respirations 30. On January 22d the temperature was 99.8°, the pulse 100, the respirations 26. No further serum-treatment was given.

On January 23d the temperature was 99°, the pulse-rate 88, the respirations 26. A few points of eruption existed on the neck and body of the size of a pin-head. The other points of eruption had dried. The man was allowed the liberty of the ward, and was given calcium sulphid gr. ij every three hours. He was discharged from the hospital February 5th. The number of injections had been five, the quantity of serum used 165 c.cm.

CASE V.—B. R., female, colored, aged sixteen years, a domestic, was admitted to the Smallpox Hospital on January 29, 1895, with the diagnosis of *variola vera*. She had been vaccinated unsuccessfully. The temperature on admission was 101.8°, the pulse 120, the respirations 34.

On January 30th, at 10 A.M., the temperature was 99 6°, the pulse 94, the respirations 36. Erup-

tions existed on the face, neck, chest, and feet. She had pharyngitis and bronchitis, with free expectoration, and she was menstruating. Under the right breast 30 c.cm. of the third supply of serum were injected. (This serum was from the blood drawn the second week after the recovery of the calf.) The tissues surrounding the point of injection became hard, swollen, and cold (3 in. × 2½ in.), and were elevated about one-half an inch, with the pits before described. There was no pain. At 1 P.M. the temperature was 100.6°, the pulse 88, the respirations 24 to 30 in the half minute, very superficial, with very little chest-movement. The point of injection was still sore. At 5 P.M. the temperature was 103.6°, the pulse-rate 112, the respirations 36 and of better character. There was still soreness at the point of the injection. At 7 P.M. the temperature was 103.2°, the pulse 102, the respirations 32. I injected 22 c.cm. into the right buttock, with the same results as in the former injection. A few papules became umbilicated.

On January 31st, 10.30 A.M., the temperature was 100.4°, the pulse 74, the respirations 22. Several pustules had filled, and were umbilicating, others had dried. I injected 15 c.cm. of serum into the left buttock, followed by the same swelling and hardness. The point of injection in right buttock was not sore, but that under the breast was sore. At 1.30 P.M. the temperature was 99°, the pulse 80, the respirations 28. At 5 P.M the axillary temperature was 98°, the tongue temperature 99°, the pulse 72, the respirations 28. At 10 P.M the temperature was 99.2°, the pulse-rate 70, the respirations 26. There were no new points of eruption.

On February 1st the temperature was 99°, the pulse 86, the respirations 28. Two small pustules had appeared on the face. The woman was given the liberty of the ward February 5th, no further serum-treatment

being instituted. The number of injections was three, and the quantity of serum used 67 c.cm.

This patient was discharged on February 22d, entirely well, but was readmitted on February 27th from the Freedmen's Hospital, with what I think was either variola vaccinæ, an unfortunate effect of the vaccine-serum, or a septic infection. Her disease went through a course of fever and eruption, followed by a number of abscesses. While I have never seen a well-marked case of cow-pox, some cases having as many as 400 pustules, I am more than positive it was either a case of cow-pox or an eruption attending a large dosage of strong serum.

CONCLUSIONS.

From my limited experience with vaccine-serum I conclude:

1st. Vaccine-serum modifies variola.

2d. Vaccine-serum has a marked influence upon the eruption of the disease, in that the papules or vesicles abort and the pustules desiccate.

3d. Vaccine-serum prevents pitting.

4th. Vaccine-serum should be accorded a place in the therapeutics of variola.

Whether or not my experience will be confirmed by that of others I cannot say; it remains for future investigators, working upon the same lines, either to prove or disprove my conclusions.