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THE TREATMENT OF SEPSIS IN SCARLATINA WITH ANTISTREPTOCOCCUS SERUM

MATTHIAS NICOLL, M.D.

NEW YORK

In using the term sepsis in scarlet fever I desire to be understood as referring to a set of clinical symptoms occurring forty-eight hours or longer after the onset of the disease, which are apparently due to the invasion of the body by organisms of the streptococcus group, which, up to the present time, are not known to possess any cultural or other characteristics which serve to distinguish them from streptococci isolated from a number of other morbid conditions. The symptoms may be briefly stated as follows: No fall of temperature, or a renewed rise; abnormal swelling of the mucous membrane of the throat, with or without superficial sloughing; profuse nasal discharge; marked cervical adenitis; rapid, often irregular pulse; mental apathy; active or low delirium. Streptococci may or may not be found in the blood, and it should be said that while they are usually present in prolonged cases especially, they are not necessarily so, even in those which must be clinically regarded as septic and, on the other hand, may be found at an early stage in cases whose course is otherwise benign and which do not admit of other than a technical diagnosis of this condition.

Until the organism which causes scarlet fever has been definitely determined we must continue to regard those cases which are overwhelmed by the onset of the disease and are likely to succumb in twenty-four to forty-eight hours as directly due to this undetermined cause. Such are, in this country at least, of comparatively infrequent occurrence. The greater number of severe and fatal cases being of the class the symptoms of which I have described.

Scientific workers on the problem of scarlet fever seem more and more inclined to disregard the possibility, formerly so generally advocated, of streptococci representing anything more than the invasion of a secondary organism on a soil suitably prepared by some unknown agent. If this view proves to be correct, it must be confessed that certain well-authenticated phenomena are thus rendered most difficult of explanation. Of these I may mention the undoubted success of vaccination with killed streptococci from scarlet fever patients as a means of preventing the latter. This work has been largely confined to Russia and apparently

has caused but little interest in this country. Of the recent reports I may mention that of Tesjakoff, who in a study of 15,000 vaccinated patients, reaches the conclusion that three inoculations extending over two weeks is able to protect against the disease. Again Raikowa, making observations in seven epidemics, on 721 vaccinated patients, found that among 524 patients vaccinated but once nine cases of scarlet fever occurred; among 122, vaccinated twice, five cases, while seventy-five patients vaccinated three times remained free from the disease.

Verhoff points out that the death-rate in 403 vaccinated patients in whom scarlet fever occurred was but 6 per cent., compared with a rate of 17.5 per cent. in the unvaccinated. Furthermore, all those who have made use of vaccination, from Gabritchewsky, who originated it, to the present, agree as to the common occurrence in those inoculated, of symptoms which cannot be distinguished from those of scarlet fever of the milder type as regards the onset, course, rash and occasional complications. Again, if the streptococcus be eliminated, how are we to account for the good results of the antiserum in Moser's fourth category of cases—those patients overwhelmed by the first rush of the disease—which showed a mortality of 100 per cent. without serum, and 65 per cent. or less with its use?

Two recent attempts to do away with the streptococcus as a causative factor are of interest. Cantecuzène, of Bucharest, reported to the Société de Biologie in April, 1911, that he had inoculated nine of the lower monkeys with bronchial glands, pericardial exudate and blood, the latter two free from streptococcus, taken from scarlet fever patients, and produced what appeared to be in all respects true scarlet fever, having an incubation period of seven to thirty-five days, and followed by typical desquamation. I am authorized by Dr. William H. Park to state that six monkeys (*Macacus rhesus*) injected with the blood of six different scarlet fever patients not tested for streptococcus, failed to show any symptoms of the disease, one dying after a few days of ileocolitis. Dr. George Bernhardt of Berlin, working under Gaffky, reported in April that by inoculating a number of lower monkeys with suspensions of tongue-scrapings, serum and enlarged nodes of scarlet fever patients, subsequently excising the enlarged inguinal nodes near the site of injection, grinding and passing the latter through other monkeys, he was finally able to procure nodes showing no streptococcus or other organism, whose further inoculation into another series of monkeys caused symptoms in all respects similar to those in scarlet fever of human beings.

If this work can be confirmed, it must be conceded that the streptococcus can no longer be regarded as the causative factor or essential to its development. Until this is accomplished it would seem wise to have an open mind on the subject, especially as it is becoming daily more evident that with greater refinement of technic and newer methods of differentiation, we may soon be able to assign to the various strains of

these organisms specific characteristics in the production of different morbid conditions, one of which may be scarlet fever.

The serum treatment of scarlet fever, first brought into prominence by Moser, whose name is usually associated with a serum produced by the inoculation into horses of streptococci taken from many patients with scarlet fever, was, like most specific remedies, hailed at first with the greatest enthusiasm, and, like most specifics, the results obtained did not fulfil popular expectations. If one consults the now fairly voluminous literature on the subject, he is sorely puzzled to account for the contradictory opinions set forth as to the worth of the serum. This, in part, is to be explained, I believe, by difference in the methods of its employment, whether used early, or only late, in moribund cases; differences in the type of the disease, not only locally, but as between different countries; and finally, by judgment founded on too few cases. There is, furthermore, undoubted difference in the antitoxic strength of sera and not unnaturally a prejudice against the use of the huge doses which seem essential to the production of results.

I shall refer to but one set of observations, those of Fedinski of Moscow, published in 1910, who in a most elaborate analysis of 317 cases in which serum was used, compared with about 900 cases without it, comes, as it seems to me, to the very reasonable conclusion that the serum given in full doses before the fifth day greatly increases the chance of recovery, even in the apparently hopeless cases; that in a large majority the temperature falls by crisis within twenty-four hours, or, if by lysis, the course of the fever is shortened. The occurrence of complications is less frequent and their gravity diminished. The influence on the heart's action, central nervous system, the rash and on necrotic processes is marked. The dosage in the average severe case was 200 c.c. subcutaneously, except in the case of young children, when 100 to 150 c.c. were given, and this dose was repeated in from twenty-four to forty-eight hours if necessary. Chart 1 shows the deaths from scarlet fever in the City of Moscow for a series of years. The solid line represents those patients who died outside the hospital, the dotted line those receiving hospital treatment. It will be noted that the average of the hospital deaths held well above those dying in the city, but that with the beginning of serum treatment in the hospitals, and especially in the second year of its use when others than the apparently hopeless patients were thus treated, the hospital patients show a death-rate well below those treated outside and without serum.

In this country the serum treatment of scarlet fever has, as far as I know, been but little tried. My own experience was obtained at the Scarlet Fever Hospital of the Department of Health of New York City during February, March and April, 1910, in the course of a very extensive epidemic of the disease. The serum used was that prepared under the direction of Dr. Park, consisting of eleven strains of streptococci from scarlet fever patients—blood, throat, glands, etc., and one of strepto-

coccus from a case of endocarditis. Owing to a somewhat limited supply at the time, it was thought advisable to give but 50 c.c. as an initial dose, which of course precludes the possibility of comparison with the European results. In so far as was possible in a badly overcrowded hospital, with overworked staff and nurses, every patient who showed markedly grave symptoms, regardless of the day of disease, was injected by the staff or myself and visited by me daily, with the exception of four cases furnished me by the resident physician. By no means all the fatal cases during these months were the patients injected, as measles, diph-

Chart 1.—The solid line shows the mortality curve from scarlet fever in Moscow from 1892 to 1897; the figures on the left show the percentage; the dotted line shows the mortality in the Vladimir-Kinderhospital during the same period under serum treatment.

theria and other complications accounted for their unfavorable progress and often death. Again, patients who, in spite of the severity of onset, seemed to be in no immediate danger, not infrequently took so sudden a turn for the worse that there was no opportunity to make use of the serum.

There were injected in all, thirty patients, of whom seventeen died; not a very brilliant showing, it must be confessed, but on analyzing the

fatalities, the poor results may be reasonably accounted for without detracting from the value of the serum. Of these seventeen cases, four patients were brought in the hospital in a moribund condition, immediately injected, and died within a few hours. Of those who were ward patients twenty-four hours or longer, one died within two hours after receiving injection, two others within twelve hours, a length of time too short to hope for any relief from a subcutaneous injection. Another patient, after seeming to respond favorably, contracted measles and ileocolitis; another measles, followed by gangrenous varicella. The condition of three others was shown to be due to a complicating diphtheria which failed to yield to large doses of antitoxin following the serum. One patient was injected late in the disease, with the hope of affecting a double mastoiditis, 100 c.c. being given intravenously. The result was inconclusive, as an operation was thought desirable. Following this, the patient received 100 c.c. subcutaneously, grew gradually weaker, with no marked lowering of the temperature, which had been exceedingly high, and died two weeks later in extreme emaciation. This leaves four patients in whom the failure of the serum must be accounted for on other grounds than those just described.

CASE 1.—H. H., aged 7, had been ill three days on admission; temperature 104.2 F., pulse 144, respiration 32; glands in the neck greatly swollen; patient looked extremely septic. The patient was given 100 c.c. of serum subcutaneously, pulse, respiration and temperature falling the next day and the temperature not going much above normal until just before death. Ten days after receiving treatment, the heart action became very unsatisfactory; the patient looked very pale and weak; stimulation seemed to have no effect, the pulse growing weaker and more irregular day by day. A few days later, the patient developed general choreic movements, followed by arthritis of the left wrist, and died three weeks after admission apparently of heart failure due to myocardial involvement.

I have the records of two cases similar to this in patients who were given 150 c.c. intravenously for a very grave mixed infection with diphtheria. The local throat symptoms cleared up readily under the combined use of antitoxin and serum, but the patients both died a week or more later, one with a very rapid heart action, and the other with a pulse which fell from 120 to 53.

CASE 2.—S. McB., aged 4, ill eight days; throat very much swollen; cervical nodes greatly enlarged; patient profoundly septic and delirious; temperature 104, pulse 180. The patient was given 50 c.c. of serum and died thirty-six hours later without any apparent amelioration of conditions. The failure of the serum in this case may be reasonably attributed to the length of time the patient was ill.

Following are two cases (3 and 4) in patients of Dr. Sexton, the resident physician, whom I did not see. They were, however, very carefully studied and the pulse and temperature taken every two hours, before and after the administration of serum.

Chart 2.

Chart 3.

Chart 2.—Shows the effect on temperature and pulse of serum administered in Case 5.

Chart 3.—Showing effect of serum treatment in Case 6.

CASE 3.—J. K., aged 2, had been ill four days on admission November 17, when the temperature was 103.4 F., pulse 140, respiration 32. This condition did not change markedly during the next five days. The cervical nodes were very much swollen; the pulse at times was imperceptible. On the ninth day of her illness she was given 50 c.c. of serum and died thirty-six hours later without any appreciable effect having been produced.

CASE 4.—J. M., aged 16, was admitted November 14. November 23 the temperature was 104.5 F., pulse not countable, respirations much increased. The next day when the 50 c.c. of serum was given the temperature was 101.2 F., pulse 180, respiration 144. The patient was markedly septic, cyanosed, and wildly delirious, heart sounds muffled, pulse hardly perceptible. Temperature the next day was 100 F., pulse 160 and of a better quality; respiration 36. On the second day his temperature dropped to 97 F., pulse to 104 and respiration to 36. The patient was still cyanosed and very delirious. Mouth and nose discharged profuse bloody secretions. The third day the patient was still delirious, though the pulse was of better quality. On November 28, four days after giving the serum, the temperature was 100 F., pulse 152, respiration 36. The color was better and the pulse of a fair quality. Nourishment was taken well; nose and mouth were still bleeding. Later in the day, the condition became suddenly worse; the patient became cyanotic and died of heart failure.

If the serum had been given in anything like sufficient quantities at an earlier stage in these two cases, it is possible that it might have been successful in its action.

Of the patients who recovered, a short history of a few will serve to show the apparently good effect of the serum.

CASE 5.—S. K. (Chart 2), aged 10; ill two days on admission; covered with an intense dusky rash with much vesiculation; throat and cervical lymph-nodes very much swollen; lips dry and fissured; constant muttering delirium; 100 c.c. of serum given subcutaneously. The next day the temperature fell; the delirium continued. The following day, 100 c.c. serum was given. There was a general and profuse desquamation over the whole body; the patient was not delirious, but very stupid. The day following there was a marked improvement in the general condition. The subsequent history was one of convalescence, interrupted by multiple arthritis in the third week. The patient was discharged in good condition after a long stay in the hospital.

CASE 6.—E. R., aged 7 (Case of Dr. Sexton). The patient had been ill six days on admission, was profoundly septic, gums and lips sloughing, teeth dropping out, eyes injected and excreting profusely, cervical nodes much swollen, patient unconscious. He was given 50 c.c. of antistreptococcus serum on the second day after admission to the hospital, when his temperature was 102.3 F., pulse 150, respiration 132. The subsequent course of his temperature and pulse is shown in chart 3.

Two days after receiving serum, the condition of the mouth and gums had very much improved. On the sixth it was noted that the patient was crying for food. On the eighth the pulse, temperature and respiration were normal and the recovery was complete.

CASE 7.—L. J. (Chart 4), aged 15, had been ill two days on admission; very toxic; vomiting was constant; throat was very much swollen, also the cervical nodes; pulse very rapid and feeble. Improvement took place in twenty-four hours, with uneventful recovery, after the administration of 100 c.c. of serum, given on the third day after her admission to the hospital.

CASE 8.—R. S. (Chart 5), aged 6½, ill two days. Dr. Sexton, who observed the case throughout, noted that the patient was wildly delirious, but did not regard her as septic. The temperature was 105.5 F., pulse imperceptible, respira-

tion 44. She was given 50 c.c. of serum on her admission to the hospital; twenty-four hours later the delirium was less marked and the temperature and pulse were down. The following day the patient's condition was excellent, delirium had ceased, and recovery was very rapid.

Chart 4.

Chart 5.

Chart 6.

Chart 4.—Effect of serum treatment in Case 7.

Chart 5.—Result of serum treatment in Case 8. Patient ill only three days.

Chart 6.—Showing drop in pulse and temperature after administration of serum in Case 9.

CASE 9.—H. S. (Chart 6), aged 10, had been ill two days on admission. The patient was very septic, with swollen throat and cervical nodes. Fifty c.c. of serum was given on the fourth day of her illness. Temperature and pulse fell by rapid lysis, and recovery was uneventful.

These examples are sufficient to illustrate the apparent effect of the serum on the pulse and temperature, and on the general and local septic conditions.

In a number of other cases in which the temperature was not so high, but in nearly all of which the pulse was very rapid, the effect of the serum was marked. The following illustrates its usefulness in local conditions about the nose and throat.

CASE 10.—S. K., aged 8½, had been ill five days on admission. The patient was apparently suffering from marked general sepsis, with profuse, foul, dark-colored nasal and oral discharge, with great swelling of the cervical nodes; lips also markedly swollen and fissured. The patient's mouth was wide open all the time. He was extremely apathetic. On the eighth day of his illness he was given 50 c.c. of serum, at which time the temperature was 101, the pulse 140. The amount of discharge from his nose and mouth was simply appalling. The temperature the next day rose 2 degrees; the pulse fell slightly. The following day the pulse fell to 110, the discharge showed very marked improvement and a few days later had ceased, the patient making an uneventful recovery.

What bad effects from the serum may be expected? In the foreign statistics rashes of various kinds occurred in a large number of cases, generally, however, of an urticarial type; also rise of temperature, evidently due to the same cause in about half the number, and occasionally polyadenitis, arthralgias and localized edemas. In my experience, I should say that with a dosage given subcutaneously, even of 50 c.c., an urticarial rash was the rule rather than the exception. Other and severer forms of rash I have not seen. A moderate rise of temperature accompanying the rash is not infrequent. Polyadenitis and arthralgias which could be definitely attributed to the serum were not noted. One case of true anaphylaxis occurred recently:

CASE 11.—P. P., aged 5, was admitted January 28, after one day's illness with scarlet fever and diphtheria. He was given 6,000 units of antitoxin on admission, and on the following day, as his throat seemed worse, 10,000 units. The patient had a tuberculous hip joint and was in generally poor condition. His subsequent history was that of chronic sepsis, with double mastoid infection, requiring operation, and abscesses in various parts of the body which when opened healed very badly.

April 17, seventy-nine days after admission to the hospital, a blood-culture was made and immediately antistreptococcus serum was allowed to run into the same vein. It ran very slowly, not more than 10 or 15 c.c. entering the vein, when the patient, who had been whimpering, gave one or two sharp coughs and attempted to vomit. The face became intensely cyanosed, and then deathly pale, except for a purple band extending across the forehead and eyes. The needle was immediately withdrawn, and the patient put to bed. He was unconscious, his color absolutely death-like; the pulse could not be felt; a dusky erythema covered the whole front of the body. The respirations, which had previously been 38 to 40, varied from 15 to 22 a minute with deep inspiration, very noisy and drawn through closed teeth. A few minutes later a purpuric rash covered the right limb from hip to ankle, the color disappearing only under long pressure. On the inside of the left leg, was a rash somewhat scarlatiniform in character.

These rashes disappeared in half an hour, except on the inner side of the right foot, where a circinate rash took the place of the purpuric. Under active stimula-

tion and heat, consciousness returned within an hour and the patient recognized those about him. There were râles at the bases of both lungs which had not been noted previously. The next day the pulse, temperature and respirations were about as they were previous to the injection. On the following day there was an exanthematous rash on the scalp, and a patch of erythema in front of the right ear. The subsequent history of the patient was one of progressive emaciation, death taking place about ten days later.

Whether these phenomena would have resulted from a subcutaneous injection I am unable to say. In another case, not scarlet fever, the patient developed a severe local anaphylaxis followed by an extensive area of sloughing at the point of inoculation following her eighteenth subcutaneous injection, the previous injections having caused nothing more than a mild urticaria. For this apparent lack of immunity to horse-serum, after seventeen injections given at short intervals, I have no explanation to offer, unless it is to be regarded as an example of the Arthus phenomenon. I have had an opportunity during the last few months to observe the effect of large doses of this serum given intravenously, and with the exception of the case mentioned I have not seen any alarming results which could be attributed to this method of administration. However, I am not prepared at this time to recommend its general use in this way, except in those cases in which a delay of twelve hours would probably determine a fatal outcome. Here, intravenous injections are by all means to be preferred.

Until there is some method of standardization and concentration of the serum, it would seem highly desirable to use a dosage believed to be essential to the best results by those who have had most experience with it, namely, for older children and adults, 200 c.c. injected, by preference, one-half into each side of the lower abdomen; for infants and young children, 100 to 150 c.c. in all.

The apparatus employed has been used for a number of years in the New York Department of Health for the inoculation of horses with large doses of serum, and I have found it most convenient for clinical purposes. It consists of a glass container, which may hold from 100 to 200 c.c., a rubber tube sufficiently long to be convenient, and a force pump which serves to give enough pressure to cause the serum to enter the tissues through the needle. It may be used equally well for intravenous injection. Care should be taken to see that the serum is heated to 100 F., otherwise a chill will result.

Finally, while my somewhat limited experience with this remedy does not entitle me to form a decided opinion, I cannot help but feel that in a disease over which we have little or no control, and which so frequently goes unexpectedly wrong, in all severe cases of scarlet fever, the serum, if attainable, should be made use of in full doses and without delay.

124 East Sixtieth Street.