

has resulted. But whatever the dangers are they must be risked when dealing with a severe streptococcic infection and it cannot be too strongly insisted on that with the serums which are at present available a large dose is necessary for any success; the dose of five cubic centimetres of antistreptococcic serum which is sometimes advised is probably quite useless and failure which is the consequence of inadequate dosage is one of the reasons why the use of antistreptococcic serum in puerperal cases has fallen into partial disrepute.

The Middlesex Hospital, W.

A CASE OF STREPTOCOCCIC PUERPERAL INFECTION TREATED WITH A SPECIAL PUERPERAL ANTISTREPTOCOCCIC SERUM; RECOVERY.

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THE case to which the following notes refer was one of an extremely severe type of streptococcic infection in which there seemed to be no doubt that ultimately recovery was due to the action of an antistreptococcic serum.

The patient, who was 29 years of age, was admitted into the Chelsea Hospital for Women on Nov. 12th, 1904. Her previous history showed that on Oct. 15th she was delivered of her third child. The puerperium and labour were normal but the latter was a little prolonged. She was attended by a midwife, and on Oct. 18th the temperature rose to $102\cdot4^{\circ}$ F. and the pulse-rate was 120. A medical practitioner was then called in and the uterus was explored but nothing was found retained. An intra-uterine douche of perchloride of mercury (1 to 4000) was given. The temperature fell and everything appeared to be going on well until Nov. 1st, when the left leg became painful and began to swell. The temperature gradually rose again and on the 5th the right leg also was swollen. When admitted into hospital on the 12th the patient was extremely ill; she was very anæmic, her temperature was 102° , and the pulse-rate was 120. There was some rigidity of the lower part of the abdominal wall but no distension or tenderness on pressure. By vaginal examination it was found that the uterus was slightly enlarged and tender; the os uteri had contracted; there was no discharge or offensive odour. There was distinct fulness in both lateral fornices. Both legs were considerably swollen and presented typically the appearance of white leg. On the 17th the temperature fell to $98\cdot4^{\circ}$, the pulse-rate was 120, but the general condition of the patient was not improved in any way. Towards the evening the temperature began to rise again and a condition of mental apathy became apparent. She gradually became worse and on the 20th the temperature was $102\cdot8^{\circ}$ and the pulse-rate was 160. On the 22nd the patient, having been delirious for two days, passed into an unconscious condition. There were sordes on the lips and urine and fæces escaped incontinently; the temperature was 102° and the pulse was uncountable. She was being fed through a nasal tube and cardiac stimulants were given freely, without, however, any improvement in the state of the pulse.

Dr. W. F. V. Bonney saw the patient on this date and advised the injection of the puerperal antistreptococcic serum suggested by Mr. A. G. R. Foulerton and doses of five cubic centimetres each were injected at noon, at 6 P.M., and at midnight. On the morning of the 23rd the temperature had fallen to 101° and the pulse-rate was 148. At noon a dose of 20 cubic centimetres of the serum was injected and at 2 A.M. on the 24th the temperature had fallen to $98\cdot2^{\circ}$ and the pulse-rate was 108. There was a most marked improvement in her general condition and she was able to take a little nourishment by the mouth. The temperature remained at the normal and progress towards recovery was uninterrupted except by the appearance of an erythematous rash on Dec. 2nd accompanied by some febrile disturbance. The rash appeared first on the abdomen, round the place at which the serum had been injected, and spread to the legs and arms; it persisted for three days, during which the temperature ranged between $98\cdot2^{\circ}$ and $99\cdot8^{\circ}$.

In this case the effect of the serum injections was well

marked. On Nov. 22nd, when the serum was first given, the patient was in a most serious condition and a fatal result was anticipated. Owing to a misapprehension rather small doses of the serum were given during the first 12 hours but distinct improvement was obvious, the temperature fell somewhat, and the pulse, hitherto uncountable, could be counted. The result of the larger dose, given 24 hours after the first injection, was very distinct, and within a few hours the patient was practically out of danger.

The case appeared to be one of pure streptococcic infection. At the commencement of the serum treatment a sterilised "swab" was passed with the usual precautions directly into the cavity of the uterus and the result of the bacteriological examination in the laboratories of the Middlesex Hospital was to prove the presence of a streptococcus in pure culture.

My thanks are due to Dr. W. H. Fenton for his kind permission to publish the details of this case, which was under his care at the hospital, and to Mr. Foulerton for placing at my disposal the special puerperal antistreptococcic serum which was used.

Chelsea Hospital for Women, S.W.

ON THE ADMINISTRATION OF ANTI-STREPTOCOCCIC SERUM.¹

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SERUM-THERAPY in many of its phases has hardly yet emerged from the experimental stage. Although recently the number of antibodies has increased and careful experiments on animals have proved their efficiency, yet there is great need for more complete observations on the effect of these serums on infective processes in the human body. We have not yet left the stage at which isolated reports of cases treated with antitoxins help towards the definition of our knowledge and each carefully observed case which is complete from the bacteriologist's point of view is of value. The following case is a record of my personal experience as a culture medium for the streptococcus. I believe that there are some points of definite value in the course and treatment of the case and have therefore ventured to give it publicity.

The source of infection was the body of a child one month old, on which a necropsy was performed on May 4th, and in which, besides suppurative epiphysitis and necrosis of the right humerus, there were infected areas in the subcutaneous cellular tissues over the left pectoral muscle, the left wrist-joint, around the left tendo Achillis, and the right popliteal space. These areas had either been incised and were dry and non-granulating or they formed reddened patches on the surface which showed an accumulation of bloody serum in the cellular tissue on incision. The child had been infected by way of the umbilical vein, for there was an encapsulated accumulation of yellow pus of about the size of a hazel nut at the transverse fissure of the liver.

No suspicion was entertained at the time of the necropsy that the hands had been cut or scratched during its performance. The same night, however, a tiny puncture was discovered at the distal joint fold of the left index finger and a carbolic dressing was applied. A small swollen area was present around this puncture next morning, but there were no signs of its spreading or of its absorption into the general circulation. At mid-day, rather less than 24 hours after the infection, there was a feeling of malaise which increased and three hours later a well-marked rigor occurred; the temperature at 4.30 P.M. was 97° F.; the axilla was now painful and on examination the lymphatics could be traced in red streaks the whole length of the arm. The axillary glands were tender but only slightly enlarged. Half an hour later the temperature had risen to 101° and at 6.30 P.M. Mr. F. F.

¹ Nearly three years have elapsed since this record was written but during this time the manuscript has been unavoidably laid aside. Further cases have been recorded in the interval but I believe that there are still points of sufficient interest in this one to merit publication and I have left my original comments on the case unaltered.

Burghard made an incision in the swollen tissues at the point of infection. At this time the finger was swollen and tense as far as the second joint. No pus was obtained from the incision, but a specimen of the blood was sent to Mr. T. J. Bokenham for examination. At the same time 25 cubic centimetres of antistreptococcic serum (Burroughs, Wellcome, and Co.) were injected beneath the skin of the abdomen; at 7.30 P.M. the temperature was 102.4°. At 9.30 P.M. it had fallen to 100.2° but later (11.45 P.M.) it was again 101°. On May 6th another ten cubic centimetres of serum were injected in the morning and the temperature fell from 100° in the morning to 98.8° in the evening. Meanwhile the swelling of the hand continued to spread, the finger was tense and glazed, and this appearance extended over the knuckles to the middle of the hand. The proximal interphalangeal joint was tensely distended with fluid. There was a patch of redness and some swelling over the back of the forearm. Ten cubic centimetres of serum were again injected in the evening. The bacteriological report stated that the infection was "a pure culture of streptococcus of very virulent nature." On the 7th the temperature remained below 99° and no further injection of serum was given. The condition of the hand and arm appeared to be stationary, but on the next day the swelling of the hand and the lymphangitis began to subside and the improvement thereafter was continuous.

Rashes.—36 hours after the first injection an erythematous rash appeared around the injection puncture and spread over the right half of the abdomen. 12 hours later a similar rash appeared round the second puncture and a similar phenomenon appeared around each succeeding puncture after a definite interval of time. The right groin and axillary glands became painful and somewhat enlarged soon after the appearance of the erythema and remained in this condition for four or five days. On May 14th there was still well-marked erythema present and a very irritating urticaria-like rash appeared over both sides of the abdomen and lasted for some hours. The right groin and axillary glands were still tender and slightly enlarged. On the 15th, after being in the country for six days on tonic treatment, acute effusion suddenly occurred in the sheaths of the tendo Achillis on both sides. This was accompanied by a feeling of malaise and slight chilliness but there was no distinct rigor. The tendon sheaths were tensely distended and extremely tender and the skin over them showed a bright red blush and the depressions behind the malleoli were puffy and filled up. The temperature stood at 99.5° at 8 P.M. On both legs a bright pink rash, formed of numerous small slightly raised spots with a slight amount of irritation, appeared just above the swollen tendon sheaths and extended over the lower third of the leg posteriorly. Ten cubic centimetres of serum were injected under the skin of the abdomen and the ankles were swathed in moist carbolic dressing.

On May 16th there were tenderness and swelling over the posterior aspect of the external condyle of the right humerus and this spread up into the lower third of the arm. A tender area of redness and swelling appeared over the head of the right ulna. On the 17th another area of swelling appeared on the front of the left forearm just above the wrist. There were some tenderness and puffiness over the condyles of the left humerus posteriorly. A bright pink rash similar to that on the legs appeared over each spot of tenderness. The temperature remained at 99.5°. Sodium salicylate, ten grains thrice daily, was commenced. On the 18th swelling took place over the tendon sheaths of the right popliteal space and this spread up into the muscles of the ham to about the middle of the thigh. A marked area of swelling also appeared over the tendon sheaths at the back of the right hand and wrist and spread rapidly and there was tenderness in the left popliteal space. Erythema appeared round the puncture on the skin of the abdomen after an interval of about 36 hours. The swelling of the tendo Achillis sheaths gradually diminished and in four days was almost gone. The other swellings lasted each from 36 to 48 hours, coming on rapidly and disappearing nearly as rapidly. The temperature throughout this second period was not above 99.5°.

At first sight this case might seem unimportant when compared with many of those reported in the medical journals of the past year or more. The temperature here was at no time alarming and the general condition was well sustained. There are, however, several features which may be considered important if only from the fact that they define

more clearly some points on which other cases have raised merely a suspicion. The infection was undoubtedly of a virulent character. The source of infection was one from which a very active growth of micro-organisms was to be expected; the onset of severe general symptoms within 24 hours while the local appearances were still insignificant, the subsequent rapid spread of inflammation along the lymphatics, together with the bacteriologist's report, all combined to accentuate the gravity of the case. The effect of the serum has, therefore, to be considered in regard to a pure streptococcal infection which had become fully established. This effect was rapid and striking. The temperature continued to rise for an hour or more after the injection. It then fell two degrees. This drop was followed by another rise two hours later, but on the next morning (eight hours later) the temperature had fallen to 100° and by the same evening it was practically normal. It might be urged that this fall was the result of the incision of the infected area, but on this point no doubt should remain, for the condition of the hand and arm was infinitely more serious after the temperature had fallen than it was during the height of the fever and the swelling continued to spread for nearly 48 hours after the temperature became normal. Such a definite and beneficial result is not always obtained in cases of septicaemia and there are many cases—not all of which reach the medical journals—in which the injection of this serum has led to little or no effect. There is, however, good reason for such disappointments.

It has been proved by experiments on animals that these antibodies are selective in their action, that to combat the toxin of each micro-organism only the serum provided by animals immunised against that organism is effective. It is not, however, always easy to obtain definite evidence in regard to the causative organism in the infective processes of the human body and without this serum-therapy must be largely empirical. The cases in which this special antitoxin has been most frequently used (if we may judge by the reports which have appeared in the medical journals) have been those of puerperal fever. In such cases it is difficult, often impossible, to obtain a precise and independent bacteriological report upon the nature of the infection. The value of antistreptococcic serum in cases of puerperal septicaemia was the subject of debate at a meeting of the British Medical Association in 1899.¹ At that time the majority of clinicians appeared to regard the method unfavourably. Dr. Herbert Spencer in opening the discussion expressed his opinion that the treatment was unscientific owing to the majority of cases of puerperal fever being due to organisms other than streptococci, that it had not reduced the mortality and that it was not free from danger. In the same year a committee of the American Gynaecological Society² reported that Marmorek's claim that his serum would cure puerperal infection was not sustained, and that thus far the only definite result of Marmorek's work was the development of a method by which the virulence of streptococci might be increased to an almost inconceivable extent. These opinions were expressed in the early days of the serum. More recent work by Lea,³ Pestalozza,⁴ and others has shown that the streptococcus is the organism most frequently found in puerperal septicaemia and many very striking cases of cure by injection of this antitoxin may be found in medical journals of recent date. One may therefore expect that when next the subject is fully discussed these views will be very materially altered or entirely refuted. What is really wanted to establish this serum on a firm basis and to gain for it the confidence alike of the practitioner and the surgeon is a series of fully reported cases of pure streptococcal infection from any source, puerperal or otherwise, bacteriologically complete and treated with antistreptococcic serum. The present case appears to me to fulfil these requirements and has therefore a definite value.

Another point in the selective affinity of streptococcus antitoxin, and one which may explain the unsatisfactory action of the serum in some proved cases of streptococcal infection, is the fact that each different variety of streptococcus produces an antitoxin which is innocuous to other members of the group. Thus, to take an instance, the streptococcus antitoxin of erysipelas may not affect the toxin produced in streptococcal puerperal fever. To obviate this drawback in the therapeutic action of the serum

¹ Brit. Med. Jour., vol. ii., 1899, p. 965.

² Philadelphia Medical Journal, June 3rd, 1899.

³ THE LANCET, June 29th, 1901, p. 1830.

⁴ Brit. Med. Jour., Epitome, Sept. 15th, 1900.

Bokenham⁵ and Denys of Louvain, working independently, have recommended the immunisation of the animals from which the serum is obtained against all the varieties of streptococcus, and several manufacturing firms have adopted this suggestion. It may therefore be expected that such serums will display a wider range of activity than others which contain merely the antitoxin of a single variety of streptococcus. Another cause of the uncertain action of the serum is pointed out by Bokenham. The antitoxin apparently loses its activity after keeping for a certain time and this observer recommends that the serum should not be more than three or four weeks old.

In the case here described the further rise of temperature after the injection of 25 cubic centimetres of the serum is in accordance with what has been observed in many other cases. In some of these the rise has been so well marked that it may be looked upon as a reaction due to the serum. There is at present no evidence to show whether or not this rise may be looked upon as a favourable sign indicating the activity of the serum but it is possible that further observations may show that the phenomenon has a definite value in prognosis.

Another interesting and important point is the secondary attack of effusion into the tendon sheaths in various parts of the body which occurred several days after the primary symptoms had subsided and while the wound in the finger was in process of healing. On looking back through the cases treated with antitoxin this renewed activity of the poison after a period of quiescence appears to be not at all uncommon. It is noted in many cases that after the temperature has fallen to normal and, convalescence being apparently established, the injections have been discontinued a rise of temperature has suddenly occurred, accompanied by a local recurrence of inflammation, by pain in the joints, phlebitis, or some such symptom. A further injection of antitoxin has in most of these cases readily controlled the symptoms but a secondary attack of this nature has been fatal in at least one case in spite of further administration of the serum. The interval at which this recrudescence has taken place has varied from three to ten days or even longer. The question naturally suggests itself, What is the condition of the streptococci during this period? Are they still circulating in the blood, their activity controlled or neutralised by the antitoxin, or has a fresh infection taken place from the primary focus, or again, to adopt the side-chain theory of Ehrlich, are these secondary attacks merely indicative of a release of the toxin from combination with the antitoxin?

A case of puerperal septicæmia recorded by Dr. Grimsdale of Liverpool⁶ throws some light on this subject. In this case the blood during the height of the fever gave a pure culture of streptococcus. The temperature fell to normal after two injections of ten cubic centimetres of the serum and remained normal for 24 hours, after which it gradually rose to 103°. During the interval of normal temperature the blood was examined bacteriologically and again gave a culture of streptococcus. The injections were resumed and a favourable result was obtained. This observation deserves more prominence than the author has given it, for not only does it disclose the fact that the streptococci are still circulating and potentially active after the general symptoms have disappeared, but it is also a very striking proof of the efficiency of the antitoxin to control their functions. One may judge from such cases that the injections of serum might be continued with benefit for a longer period after the temperature has returned to normal than has hitherto been the custom, and further, that such patients should be carefully watched during convalescence and that in country districts serum should be kept at hand. Salicylates have apparently a beneficial effect on a number of these cases.

There can be little doubt that the most powerful effect of the serum is obtained by injection in the earliest stages of the infection. In my own case the early and rapid convalescence is to be attributed to the prompt use of the antitoxin. Even in the later stages strikingly beneficial results have been obtained but there must be many unrecorded cases in which this resort to the serum at the eleventh hour has proved unavailing. One practitioner confesses with commendable frankness that he was deterred from using the serum for some days by a perusal of the note of directions issued with the antitoxin. The note ran as follows: "In the present state of our knowledge it may be questioned whether the serum treatment of streptococcal infection should be

continued, although some apparently encouraging results have been obtained in this country." The pessimistic tone of this note was no doubt the result of the reports on the earlier cases, in some of which disastrous results were attributed to the use of the serum. Without discussing how far the responsibility for these results rested with the serum it may be said that in the more recently published cases no further ill-effects than a local erythema or an irritating urticaria and in one case "circulatory depression" have been recorded. Blumberg⁷ tells us that even these skin affections may be avoided if the serum be injected entirely into the subcutaneous tissue.

Dosage.—A good result has been ascribed to a single dose of ten cubic centimetres but the total amount used in most cases has varied from 30 to 80 cubic centimetres. In my case Mr. Burghard injected 25 cubic centimetres immediately and ten cubic centimetres for the next two days, a further dose of ten cubic centimetres being used on effusion into the tendon sheaths. No ill-effect followed the injection of 80 cubic centimetres in daily doses of ten cubic centimetres in a woman 71 years of age suffering from very severe erysipelas of the face and scalp.⁸ Dr. Victor Bonney⁹ injected 420 cubic centimetres in 42 injections during 17 days in an obscure case of septicæmia. In another case recorded by Dr. Harold Low¹⁰ 263 cubic centimetres were used altogether, 67 cubic centimetres being injected in 24 hours.

The question of dosage must, of course, be judged by the nature of each case and the effect obtained by the injection, but it is important to know that large doses spread over several days have been used without ill-effect, the more so that the following note is issued in regard to dosage by the makers: "The dose mentioned (10 c.c.) is recorded as one which has been administered with apparent benefit; but it is not stated in the sense of a distinct recommendation. All responsibility for dose rests upon the medical practitioner." The most rational method would seem to be that of a large injection (from 20 to 25 cubic centimetres) on the first occasion, followed by smaller doses as the case may require, and one must further remember that, as has been pointed out above, there is danger of recrudescence if the administration be too early stopped.

The following conclusions may be drawn from this and other recently reported cases and investigations:—

1. That injection of antistreptococcal serum in cases of pure streptococcal infection has been followed by strikingly beneficial results.
2. That variability in the results of the serum in proved streptococcal infection has been due to the selective activity displayed by the antitoxin of each variety of streptococcus or to the serum being used too late in the case or having lost its activity from staleness.
3. That more uniform results are likely to be obtained from the present "compound" antistreptococcal serum than from the earlier forms, from the prompt injection of serum at the commencement instead of near the close of a severe infection, and from the use only of serum which has been recently prepared.
4. That the initial dose may with benefit be increased and that a large quantity spread over several days causes no ill-effect.
5. That the administration of the serum should be continued for some days after the general symptoms have disappeared and a recrudescence thus avoided.

Cavendish-place, W.

Clinical Notes: MEDICAL, SURGICAL, OBSTETRICAL, AND THERAPEUTICAL.

SPONTANEOUS RUPTURE OF THE HEART IN AN INSANE PATIENT.

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THIS is a rare occurrence considering the frequency of degeneration of the heart muscle in the insane. According to the returns of the causes of death in the reports of the

⁷ Berliner Klinische Wochenschrift, Feb. 4th, 1901.

⁸ Brit. Med. Jour., vol. i., 1901, p. 1078.

⁹ Ibid., vol. i., 1900, p. 1342.

¹⁰ THE LANCET, March 19th, 1898, p. 780.

⁵ Brit. Med. Jour., vol. ii., 1900, p. 1078.

⁶ THE LANCET, Jan. 21st, 1899, p. 165.