

ANTISTREPTOCOCCUS SERUM

AS A PROPHYLACTIC AND CURATIVE AGENT .

With special reference to its use in the treatment
of diffuse cellulitis.

B Y

J A M E S R O D G E R W A T S O N .

M.A., B.Sc., Edin., D.P.H., Camb.
M.B., C.M., (With second-class honours) 1895.

-----ooOoo-----



I N D E X ..

	<u>Page.</u>
Introduction.	1.
Its Use in Erysipelas	10.
In medical and surgical Septiphlegmons (with case)	13.
In Scarlet Fever.	31.
In Diphtheria	33.
In Puerperal Fever.	34.
General Conclusions	43.

Introduction.

With a view to a better appreciation of the nature of antistreptococcus serum and a better appreciation of the place it at present holds as a prophylactic and curative agent, and the probable extension of its field of usefulness as our knowledge is added to, it is well to consider in the first place some general questions as to the nature of the organisms to be dealt with and the bearing of this particular serum towards serum-therapy in general.

The importance of the recognition of the streptococcus pyogenes bacteriologically renders a knowledge of its various characters a necessity. It is a pyogenic organism frequently found in abscesses, rapidly spreading inflammations and in some cases of puerperal fever, endocarditis, cerebrospinal meningitis, etc. How closely the streptococcus of Erysipelas, that of scarlatina, etc. are related to the Streptococcus Pyogenes is still a vexed question. Reference will be made to them later on. The characters of the Streptococcus Pyogenes which I have gathered from various sources and from personal ob-

ervation are as follows. They present small globular cells arranged in chains of varying length. They can be stained by ordinary aniline stains or by Gram's method. Perhaps the prettiest microscopic specimens of the chains are got by using Fuchsin as a stain. They produce no spores but occasionally some member of a chain presents itself as of larger size than the others, supposed by some to be cocci on the point of dividing. The cocci are immotile, do not liquefy gelatine, are of slow growth, growing best at a temperature of 37° C. They show the most perfect and longest chains when grown in fluid media such as bouillon. In gelatine-plate colony there appear in three or four days small whitish or greyish dots, never larger than the size of a pin's head - in this slow growth contrasting with staphylococci, a growth of which can be recognised on the second day. Under the low-power they are round yellowish-brown heaps with sharp, smooth edges and granular surface, sometimes ring-shaped. A gelatine stab shews small white globular granules which usually remain isolated. An

Agar-streak culture shews numerous tiny round drops that usually do not coalesce. Potatoes show no distinct growth. Bouillon becomes cloudy - the clouds later sink to the bottom.

There are two distinct forms of microbic disease from the point of view of the part taken by the microbes themselves. Firstly, we have the diseases in which the microbes are localised at or near the site of infection, never getting further afield. In these the dire effects of the microbes are due to a poison produced by the microbe, which poison gets absorbed into the system. Next we have the diseases in which the microbes are not only found at the point of entrance but can be demonstrated in various positions at different parts of the body, it may be in particular organs, or in the tissues or the bloodstream. Here the effects seem to be due to the presence of the microbe itself, the toxic effects being proportionately small; the presence of a toxin being in some cases at least doubtful.

Inasmuch as there are these two essentially

4.

different forms of organismal disease, there is of necessity an equally marked difference in the serum of the affected animals in the two cases - thus the serum in the first case has been beyond a doubt proved to have an immunising property from its truly antitoxic power against the toxin that has been elaborated by the organisms, in the latter on the other hand the immunity produced may not be due to any antitoxic power of the serum or only in part so - in those in which no separable toxin has been demonstrated we cannot say it is - but may be due to an inhibitory influence over the growth of the organisms themselves - an anti-organismal as opposed to an antitoxic power. Starting with these data we can see that there follows an essential difference likewise in the mode of preparation of the various serums and a corresponding difference in the effect that we can reasonably expect the various serums to have in the two cases when used for prophylactic and curative purposes. Thus in the cases in which the microbes are local and the general effects are of the nature of an intoxication


by the toxins produced, the serum is prepared by a separation of the toxin from a virulent growth of the organisms outside the animal body, by injection of gradually increasing doses of this toxic substance into a healthy animal until its blood-serum is rendered antitoxic i.e. becomes possessed of a power of neutralising the particular toxin which the animal has had injected. The serum of the animal is then separated and sterilised and can be used to confer immunity on other animals threatened with, or suffering from the effects of the corresponding toxin. Here the serum is truly antitoxic i.e. inimical to the toxin but it is also as might naturally be expected bactericidal in the sense that it is inimical to the bacteria by neutralising their toxins, so rendering the bacteria harmless. Though "bactericidal" is sometimes used in this sense "anti-microbic" seems to me a less objectionable term to use in this sense, although there is no single good word for it. Such a serum has been prepared for Diphtheria and Tetanus. On the other hand in microbic diseases in which the

toxin plays only a small part or in which a separable toxin is as yet only a matter of conjecture, the serum is prepared after an entirely different method.

Here living cultures of a specific microbe are injected into animals, not separated toxins, and the serum gets altered as in the former case in such a way that it confers immunity but it may be only very slightly through an antitoxic power, it is probably mainly through a bactericidal power. But there is still some doubt as to how far this is true. On this subject compare the recent experiments of Parascondolo commented upon later. Such a serum has been prepared for Typhoid fever, cholera, pneumonia, and plague.

Streptococci probably belong to the second class of organisms. Experiments on animals go to shew this. Klein (Microorganisms and disease 3rd Edition p.146) shows that if large doses of streptococci are given to an animal septicaemia and death result with plugging of the capillaries in the parenchymatous viscera with masses of streptococci, and

from the blood and spleen colonies of streptococci can be cultivated. Cultures can similarly with great facility be made from the spleen in a fatal case of septicaemia in the human subject. Antistreptococcus serum as at present in use belongs to the second class of serums. The Lyons serum prepared after Marmorek's method is from horses immunised against the streptococcus by means of highly virulent cultures of streptococci and, as belonging to this category, that its effect is probably germicidal is the view of most authorities not truly antitoxic or at least not proven to be so ⁱⁿ whole or in part. As Muir and Ritchie (Manual of Bacteriology) state it - it is antimicrobial and has little antitoxic power, i.e. can only protect from a comparatively small dose of toxin obtained by filtration of cultures. Continuing, Klein says that it is an easily ascertained fact that the Streptococcus Pyogenes cultivated from phlegmon and various purulent exudations when tested on the animal does not behave in a uniform manner inasmuch as in some instances it acts virulently.....



whereas in others it has no appreciable pathogenic action under the same conditions. Klein, however, does not make any attempt to explain this. It seems to me comparable with the well known fact that cultures of the Diphtheria bacillus e.g. in bouillon do not always, when made under identical conditions, produce a toxin of the same strength, sometimes indeed being very far from it. This it seems to me can only be explained by the supposition that there are essential differences in the organisms themselves, that is of course if the antitoxic power of the serum has been accurately gauged and the difference is not due to the variations in the natural susceptibility to the toxin in the patient into whom it may be injected. Somewhat similar is the fact that chemists engaged in the preparation of the serums have found that the completeness of immunity in an animal and the curative power of its serum are by no means parallel - its curative power does not vary *pari passu* with the immunity, as it is found that some animals in which the immunity is practically complete give a

serum of only a very low degree of curative power. This does not agree with what Klein (ibid. p.577) lays down as a "general law" if what he says be taken literally. He says "we may take it as a general law that an animal can be immunised against a particular toxin and that its blood and its blood-serum thereby acquire a proportionate specific antitoxic potency". It is what from a study of serum-therapeutics one would imagine a priori to be theoretically true but against it we have the practical experience of those chemists who prepare such serums and the anomaly can only be explained by some individual difference in the organisms employed on different occasions.

In the directions issued by Messrs Mérieux and Carré in connection with the Lyons antistreptococcus serum prepared after Marmorek's method, the serum is recommended for use in "Erysipelas, Puerperal fever, medical and surgical septiphlegmons, angina, bronchopneumonia, etc., as well as in other diseases which assume an exceptional gravity by the combination of their specific bacilli with the streptococci viz.

Diphtheria, Scarlatina, Influenza, Typhoid fever and Tuberculosis." The evidence of its usefulness in the latter three is virtually nil, but we will pass the others in review and see what evidence there is in its favour and the limitations and conditions under which it is advisable to use it and necessary to use it before we can hope to have a reasonable and scientific use of it. Special reference will be made to its value in cases of diffuse cellulitis with a case that came under my care which was successfully treated in this way.

In Erysipelas:- It is notable that Marmorek has treated with antistreptococcic serum 411 cases of various streptococcic affections with a mortality of 3.4%. Of these 45 were of Erysipelas and he says that in sufficient dose relief was felt in from 5 to 12 hours, headache and muscular pains were lessened, sleep restored and the temperature lowered. Two or three hours after injection there was a rise of temperature, later it was lowered. When done early a single dose seems to abort it, if further advanced

the fever goes less rapidly and proves specially tenacious in ambulatory erysipelas. Local betterment takes place according to the severity, time of injection and quantity of serum used.

Dr. Steele of Plaistow (Brit. Med. Jour. Dec. 7 1895) treated a case of the specially fatal form known as "Erysipelas Neonatorum". where the disease had advanced far. He had seen in a similar case recover and gives the serum all the credit. There was no other treatment used. After the first injection he noticed the temperature gradually came down to normal but it did not prevent a second patch appearing, which extension however did not raise the temperature again as might have been expected apart from the serum.

Gonin (Lyon Médicale Feb. 23, 1896) reports a case of facial erysipelas in which the temperature fell in 24 hours 3.6° F, and 48 hours cut short the attack.

McGregor Young (Brit. Med. Jour. 1897) reports a similar case from which he could not draw definite conclusions but remarks that resolution of

facial erysipelas on the third day is not common, and as in Steele's case a new reinfection did not raise the temperature, nor prevent general improvement. On the other hand the first dose did not confer immunity against even an immediate second attack nor did the second dose prevent the streptococci from pushing their way over the site of injection which though deep we might reasonably have expected to have charged the lymphatics overlying with bactericidal serum.

Chantemesse used Marmorek's serum in 501 cases and had a total mortality of $2\frac{1}{2}\%$, whereas his cases treated in the ordinary symptomatic way had a mortality of from 3 to 4%. He says that he considers that the good effect of the serum is in direct proportion to the strength of serum - a preventive potency of 1 in 30,000 being best.

Marmorek's and Chantemesse's results have the advantage of including a large number of cases. The other cases recorded, however, have enough of their results in common to warrant us in accepting them as a proof that the serum if used in a larger number of

cases would prove itself fit to occupy the high position that these recorded cases would give it in lowering the death-rate and diminishing the ill-effects of the more severe non-fatal cases.

Antistreptococcus serum in medical and surgical
septiphlegmons:-

Notes of a case of rapidly spreading diffuse cellulitis treated with antistreptococcus serum by
J. R. Watson, M.B., Hamilton. N.B.:-

J. H. aet. 38, a mining contractor, got his right little finger badly crushed and broken on 3rd. December, 1897 by a large stone falling on it. The finger became very painful and from the 6th to the 10th he poulticed it with bran poultices but the pain only increased. When I saw him for the first time on Dec. 10th the little finger and back of the hand were much swollen and a small bead of pus was escaping from the front of the little finger. It was now opened thoroughly and washed out with an antiseptic lotion. This relieved him greatly and he slept well

for the first time since the 5th. Next day the swelling had extended to the limit of the common flexor sheath above the wrist and pain was again coming on. The sheath was accordingly opened into, in front of and behind the anterior annular ligament, a drainage tube inserted and the whole sheath washed thoroughly out. From this time onward he had no pain to speak of. In the sheath there was a great amount of pus, very thick, which on bacteriological examination revealed the streptococcus Pyogenes in almost pure culture. The swelling was very intense but at that time stopped abruptly at the limit of the flexor sheath. The temperature at this time was 103⁰ F. But the mischief had extended even further than was apparent; for next morning there was an extremely tense brawny swelling of the whole forearm to the elbow. The diffuseness of the swelling and the want of any point of softening rendered an other single opening impracticable and to lay open every space where the inflammation may be in such a case seems to me to be, in the lower class of private practice

at least, a hopeless task. Various expedients were accordingly tried to soften the hardness, the most successful being the application of carbolic poultices to encourage the breaking down. Under this treatment the temperature which had till then ranged between 101 and 103^o F. from the time I first saw him steadily decreased till the morning of the 16th when it was 98.6 or virtually normal. (The temperature had probably been even higher than 103 before I saw him - he was extremely emaciated and seemed to be very weak and he seemed to be scarcely responsible for his actions, threatening to take away his own life, etc. This quite disappeared after the hand was opened). The same night, however, (16th) his temperature rose again to 102.5. He had a bad headache, a dry tongue and great thirst. A similar swelling to what was in the forearm had also appeared along the inner side of the upper arm with intense local heat. As there was by this time antistreptococcic serum at hand (Lyons; preventive potency 1 in 30,000) this seemed a suitable time to test its

efficacy in such a case. 10cc. were accordingly injected that night. Next morning his temperature was 99.2 and the swelling in the upper arm had considerably abated and the intensity of the heat had diminished. He had slept well, took a hearty breakfast, his headache had gone and the tongue was moist. Another dose of 10cc was given. That night (17th) his temperature was 100 and in the morning 99.5. and there could not be detected a single trace of any mischief in the upper arm nor did any such reappear. Though several fresh openings were made in the hand, no further opening was made in the forearm. There was all along free discharge from the tube at the wrist, removal of discharge from the forearm being encouraged at each dressing by pressure towards the wrist, a few small sloughs were discharged at the wrist, the whole swelling gradually softened and disappeared, remaining much longest in the hand. Mercury ointment aided the disappearance of the oedema which persisted in the hand and he recovered with every joint intact and with a useful hand.

(Vide Temperature Chart)

From before the time of the first injection there was no medicinal treatment except that from the 16th to the 26th a quantity of alcohol was given each day in the hope of enabling the system the better to withstand the septic poison (vide Binz' Pharmacology New Sydenham Society - Vol.I p.333).

The local effects of the injections were almost nil - he described it as a feeling "as if he had been kicked there a few days ago". They were given between the scapulae. The general effects were that the temperature was raised temporarily for a few hours, then lowered. There was also in this case an intense diaphoresis about five hours after each injection, but this may have been an individual peculiarity as I fail to find it recorded in other cases in which the serum was used.

From the experience of this case I would judge that the serum is eminently useful in checking incipient streptococcic inflammation but that its use beyond this is very doubtful as there was no improve-

ment in the condition of the forearm that might not quite well be attributed to the local treatment it received, whereas the upper arm received no local treatment whatsoever. If this be the true state of matters, probably the mischief in the forearm might likewise have been aborted by a timely injection at the time the sheath was opened had there been serum at hand, but after the forearm was thoroughly implicated until the 16th the temperature was coming down and the general condition improving so that to have given the serum at any period during that time would have given one a very hazy notion of its efficacy. I am of opinion that the serum if given sufficiently early in such cases of hard brawny swelling may make it disappear and if not early enough for this may at least make incisions in the early stage before it has broken down less necessary and even this is a great boon as incisions at that stage we know are very unsatisfactory, affording little relief. We may take it as a fact, though there is not such a body of statistics to prove it as in the case of Diphtheria that

the main desiderata in such cases are, as there, an early bacteriological examination and, should that prove positive, an early use of the serum. In connection with this case I should like to say a word as to the probable origin of the streptococci. The poultice he removed when I first saw him had a sickening, sour, offensive odour and this case illustrates in my opinion the immense danger one may run by applying to a broken surface a septic poultice such as he had used.

There are one or two more points of interest raised by this case. - Among other remedies tried for softening the brawny swelling was Ichthyol. This remedy so useful in the more superficial forms of streptococcic inflammation was found to be almost useless. The fact that the ordinary treatment for Erysipelas, local and general, does not visibly improve those deeper cellulitic inflammations which have as in this case been proved beyond a doubt to be streptococcic might be taken as a point in favour of the dictum of Klein that "no matter how much they resemble

each other morphologically and culturally the Streptococcus Pyogenes and the Streptococcus Erysipelatos are essentially distinct organisms", but it may be simply that it cannot reach the deeper inflammation as it can the more superficial and besides all observers do not agree with Klein. Muir and Ritchie (ibid. p.155) say that recent study goes to show that they are one and the same organisms and especially the results of modifying the virulence go to shew this, cutaneous Erysipelatos being produced when the Streptococcus Pyogenes of a certain standard of virulence gains entrance to the lymphatics of the skin. Compare also the experiments of Marmorek and of Petruschky quoted below.

The fact (if we may look upon it as a fact) that it is on incipient streptococcic inflammation that the serum shows its effect seems at first sight to be a point in favour of the argument that the action of the serum is mainly an anti-microbic one not a true anti-toxic one, but it is not necessarily so, because statistics show that the earlier the inject-

ion of anti-diphtheritic serum in diphtheria, the better are the results, and in the case of anti-diphtheritic serum we know that the action is certainly strictly antitoxic (vide the Returns of the Metrop. Asylums Board Hospitals). On the other hand one cannot but think, considering the wide diversity of cases in which Marmorek's serum has been alleged to have proved useful that there may be an antitoxic element in it also. The Streptococcus Pyogenes and Erysipelatos the Pneumococcus and the Bacillus Typhosus are all held by some authorities to have a pyogenic property apart from their specific action, and this suggests that there may be, in all these, some toxin elaborated as the result of this pyogenic property and this may explain to some extent the benefit derived from Marmorek's serum in such widely diverse affections as diffuse cellulitis and Erysipelas on the one hand and Pneumonia and Enteric fever on the other, apart altogether from those cases of Pneumonia, Enteric, etc., in which the complication of the presence of streptococci is demonstrable by bacteriological diagnosis.

In other words in cases so complicated the whole improvement under the serum may not be due to a bactericidal effect on the streptococci present but may also be in part owing to a true antitoxic effect against the toxin produced by the specific microbes of the disease in their capacity as pyogenic organisms.

A case of blood-poisoning treated by this serum was recorded by Boake in Brit. Med. Jour. Feb. 27, 1897. It is a case which compared and contrasted with mine gives some very interesting resemblances and differences. His case started in a whitlow of the thumb, mine in the little finger. Boake used the serum of the British Institute of Preventive Medicine. I used the Lyons-Marmorek serum. The treatment in the two cases apart from the serum was considerably different. Recognising the hopelessness of opening such an intensely swollen forearm I made no opening above the one at the wrist. In his case Boake made free incisions in the forearm and inserted drainage tubes. He went on the principle of attempting free opening and free drainage, but I hold that in the

early stage of such a cellulitis when the whole corium is densely infiltrated and there is an intense persistent accompanying oedema one has no chance to do much good thereby as it cuts "like a potato" and tension is relieved only to a very limited degree and there is little or nothing to drain away. I went on the principle of using the serum in the hope of its stopping extension of the mischief, making a free opening so as to let free what was evidently a large accumulation of pus, very frequent dressing to get rid of the discharge and encouraging the breaking down of the swelling which was comparatively recent and yet of too long standing to be acted upon by the serum. My case recovered with his hand intact and useful, even the little finger in which the mischief originated. Boake had to amputate above the elbow and even thereafter the patient died. Boake could not decide whether the rapid disappearance of the swelling above the elbow was due to the use of the serum or to the surgical treatment - incisions and drainage - but in my case I think it must be clear that it was due to the

serum and that alone as there was no incision nearer than the wrist and the intense swelling of the forearm I knew only too well prevented drainage from the upper arm, besides in such an early stage there is nothing to drain - if there were it would have gone in the direction of the least resistance viz., further up the arm.

Watson Cheyne (Practitioner Apr. 1897) says in such cases irremediable damage is done to the body before the immunising material has time to produce its effect, or as in two of his own cases though the local process is arrested the general temperature is not improved nor is life preserved. There are now cases on record that shew that "irremediable" is a strong word to use in this relation and that "the temperature is not improved nor life preserved" is also in the light of other recorded cases scarcely a warrantable statement. In my case though the temperature did not come down to normal permanently for close on a fortnight it was never during that time so high as it had been at the first and even though it could be

proved that the serum does no good at all beyond preventing extension, in many cases that may mean that life will be preserved which would otherwise succumb. He goes on to say that experimental evidence is strongly in favour of prophylactic injections and that it is in prophylaxis that it will be found most useful, in particular in serious operations about the mouth so as to prevent the chance of septic pneumonia so apt to follow such operations. I entirely agree that it is in prophylaxis that it will find its greatest use but this should not preclude us from its use even after the affection is so far advanced, for in such cases as those above of diffuse cellulitis however far the damage may have been done, so long as the patient has not succumbed to it - at the spreading part the mischief is only incipient and the serum will abort it and prevent extension, so that in no case is it advisable to refrain from its use.

Heatherley (Brit. Med. Jour. 1895) records a case of cellulitis affecting the face and neck. Though fatal eventually the serum was deemed to lessen

the swelling at a time when in the ordinary course extension and earlier death might reasonably have been expected. It was found to be due to a staphylococcus.

Ballance and Abbott(Ibid 1896) record a case of acute haemorrhagic septicaemia. The results of the serum were that the mind became clearer notwithstanding the high temperature, the frontal headache ceased, the tongue cleaned and got moist, the pulse got slower and of better quality, the respiration became slower and jerkiness disappeared, the skin became moist and sweating occurred and the wounds healed without suppuration. Nearly all these I found confirmed in my case of cellulitis. So pleased were Ballance and Abbott with these results that they recommend its use in severe surgical conditions and suggest in particular its use in fracture of the skull with risk of suppurative meningitis, acute necrosis, acute septicaemia or pyaemia from any cause, rapidly spreading gangrene or cellulitis, erysipelas, general suppurative peritonitis and septic complications of middle-ear disease. This however is set forth by

the authors only in the way of a recommendation without any statement of how far they have evidence in support of such recommendation in any one of these in particular, and to many there is no doubt it must seem too sweeping to accept without qualification. If antistreptococcus serum is not antitoxic but only "anti-microbic for streptococci" we cannot include all cases under these various names as likely to be benefited by its use but only those cases in which a careful bacteriological diagnosis reveals the streptococci e.g. it has been proved by careful bacteriologists that all cases of septic middle-ear complications do not reveal the streptococcus, so that unless the serum has an antitoxic effect likewise upon a toxin elaborated by other pyogenic organisms no benefit could reasonably be looked for from ^{its} employment.

Coleman and Wakeling (Ibid, Sep. 12, 1896) in recording a case of acute septicaemia confirm the results of Ballance and Abbott.

Steele (Ibid. Dec. 10, 1896) records a case of acute spreading gangrene in which streptococci

were proved to be abundant in the spreading margin of the gangrene and phagoedenic ulcers, and intense local treatment did not stop it, whereas the serum did, and even when the temperature was still high the general condition improved under it.

Law (Ibid. Jan. 2, 1897) records a case of general peritonitis with septic metritis which would probably have been fatal, but recovered after use of the serum, - it would probably have been fatal (as there was general septic peritonitis established before the serum was commenced) unless very stringent surgical measures had been adopted and this was not done in this case.

Crossing and Webber (Ibid. Jan. 23, 1897) put on record a case of severe acute septicaemia which was fatal and they call attention to the fact that this result was probably due to too late injection and the small doses given.

Jameson (Ibid.) holds from the experience of a case reported there that a use for the serum preferably in small doses can be found in chronic septic discharge, but this is one of the many cases recorded

in which there is no mention of a bacteriological identification of the streptococcus and until in every case there is such an examination made, whether the serum appears to be of benefit or not, we cannot hope to gain a proper idea of the action of the serum and its relation to purely streptococcic as opposed to other septic conditions.

Parascondolo (Weiner Klinische Wochenschrift No. 38 and 39, 1897) says that all streptococci are essentially different and require different serums; so also Van de Velde (Archiv. de Méd. Experimentale Tom, IX. No.4, 1897); thus that Erysipelas requires a serum prepared from the streptococcus Erysipelatos. He also says that toxins he has prepared from cultures give better serums than the living cultures themselves. But how is this explained if Marmorek's serum has shown undoubted evidence of its usefulness in these widely different cases? The Lyons serum e.g. is not warranted to be made from cultures of any particular streptococcus. In the case of Erysipelas it is not a special erysipelas-serum that is supplied but simply

what is said to be the serum of horses immunised against "the streptococcus" by means of highly virulent cultures of "streptococci". Against this are also the experiments of Marmorek and of Petruschky (Zeitsch. f. Hygiene Bd. XXII.) which shew that the same streptococcus may produce at one time a passing local redness, a local suppuration, a spreading erysipelatous condition or a general septicaemic infection according as its virulence is artificially increased by growing it alternately in serum-bouillon and in the body of a rabbit and these experiments explain so far the great diversity of lesions in the human subject with which streptococci are associated (Muir and Ritchie) and I would add too this explains to some extent the usefulness of the serum in affections with very widely diverse manifestations. Again that "toxins of these various streptococci are more potent in producing immunising serum than cultures are" has not been verified by other observers, and certainly if all the streptococci are specifically different and a serum immunised against one species has no immunising effect against any other and the toxins produced by each are

quite independent and have no relation to one another, there are many cases hitherto recorded in which the benefit derived apparently from the use of serum that has not been thus ^{differentially} ~~sufficiently~~ prepared is altogether inexplicable. If the Lyons serum be prepared by means of cultures of the Streptococcus Pyogenes, that would explain its usefulness in my case of cellulitis recorded above and in other similar cases, but would not explain its apparent success in Marmorek's or Chantemesse's cases of Erysipelas, etc., i.e. taking it for granted that the Streptococcus Pyogenes and Erysipelatos are quite distinct as Klein holds and as Parascondolo does to start with nor would it explain Heatherley's case above which was found to be due to a staphylococcus.

In Scarlet Fever;-

The use of antistreptococcus serum in the treatment of Scarlet fever still stands in a very insecure position. In the cases in which it has been thought to be of value it is in the prevention and ^{of} cure ~~for~~ secondary complications that its value has

been apparent. Klein, however, has separated his streptococcus of Scarlatina in only a "certain proportion" of cases and only during the acute febrile stage of the disease and he accordingly points out that the capability of this streptococcus to produce the secondary complications of Scarlatina has yet to be proved, although in a large percentage of cases when injected into rodents it produces acute septicaemic infection.

Marmorek (Jour. de Médecine Mar. 1896) held that the serum made swollen glands subside and none suppurated, and it seemed to cause the disappearance of albuminuria.

Baginsky (Berliner Klinische Wochenschrift April 1896) said the complications are due to the ordinary streptococcus and that there is a close relation between that and the streptococcus of Scarlatina. The serum seemed in many cases to reduce the temperature rapidly and make suppurative otitis and nephritis less common complications.

Josias (Semaine Médicale May, 1896) found these were not upheld by his cases, the serum did not

lessen suppuration, etc., Rappapert was of the same opinion judging from his cases.

The unsatisfactory position the serum holds in the case of Scarlatina no doubt rests on the unsatisfactory position the bacteriology of Scarlatina itself at present holds and is but another proof of the uselessness of serum-therapy apart from an accurate bacteriology.

In Diphtheria:-

The employment of the serum in the treatment of diphtheritic cases is also as yet highly unsatisfactory. Its use is based on the observation of Löffler that in faucial diphtheria and associated with the diphtheria bacillus occur streptococci, some of which play an important part in the secondary infections such as swollen glands, etc. These streptococci when injected into animals cause occasionally disseminated inflammatory foci, principally in the joints, and general septicaemic infection.

Sevestre (Semaine Médicale Feb. 1896) says that the accidents after injection of Roux's anti-diphtheritic serum e.g. vomiting, fever, articular

pains, eruptions, etc., are due to the presence of these streptococci and suggests the use of both the anti-diphtheritic and antistreptococcus serum in these cases but the clinical evidence of the success of this is as yet very meagre.

In Puerperal Fever;-

Much conflicting evidence has been brought forward within the last two years in connection with the treatment of puerperal infection by this serum. Much of its conflicting nature is no doubt due in great part to the complete absence of bacteriological examination in many cases, and the serum being used in many cases which were not streptococcic at all, while many of the cases may have been in reality complicated ones in which though the streptococcus was recognised, the usefulness of the serum has been hampered or altogether prevented by the presence of other organisms over and above the streptococcus.

One of the most instructive papers on this subject and one which shows to advantage the great value of accurate cultural diagnosis is that by Haul-

tain (Trans. Edin. Obstet. Soc. Vol. XXII 1897). He there describes three cases. The cervical discharge in one case revealed Löffler's bacillus in nearly pure culture and the case yielded to antidiphtheritic serum being indeed a true case of intra-uterine diphtheria. Another case showed a mixed growth of Bacillus Coli Communis and Streptococci and was fatal, the anti-streptococcus serum being of no benefit. A pure growth of Bacillus Coli was got from the blood before death. The third case showed only streptococci and the intra-uterine douching here produced no improvement till combined with the anti-streptococcus serum. Marmorek showed that the effect of the serum was less in mixed infection, especially if Bacillus Coli was present and Haultain corroborates this. Culture-diagnosis ought in fact to be the crux for the use of the serum and it is certain that different cases require different serums and in some cases one serum only may have little effect. Haultain says, however, "As in diphtheria so in sapraemia we have an antitoxin which combats only the poisonous products of specific germs, and so far it is probable that the antistrep-

Staphylococcus serum of Marmorek is of benefit. But it has yet to be shown that this serum has bactericidal as well as merely antitoxic properties before much can be expected of it", and again in his summary he says "the proof (of its benefit) practically rests in the demonstration of its bactericidal as well as its antitoxic properties". Unless he is using the terms in other than their usual sense the above is against all the evidence of the expert bacteriologists and chemists who have worked with the serum. It is in fact in direct opposition to what has been generally agreed on - viz. that the serum has an anti-microbic power and very little (if any) antitoxic power. Kanthack e.g. (Brit. Med. Jour. Feb.5, 1898) gives it as his opinion that "in time to come an antitoxic antistreptococcus serum might be obtained, at present there was none".

Still other authorities say that neither a bactericidal nor an antitoxic action have been definitely proved in the case of this serum. e.g. Bokenham in his paper before the Pathological Society in Jan.

1898 (Brit. Med. Jour. Feb. 12, 1898). As far as can be said at present it is probable that most of the antistreptococcic serums in use have bactericidal rather than antitoxic properties. It is possible, however, that though there may be essential differences in various streptococci, yet the poisons produced by them may be essentially of the same nature and may be counteracted by a single antitoxin common to them all. Calmette's researches with reference to animal poisons lend some support to such an idea, as he has proved that the poisons of different serpents and other animals, while differing in their action upon animals are yet counteracted by one antivenin. Hence this would seem to indicate the desirability of having an antitoxic serum for streptococcic affections.

Compare with these notes my remarks on the possibility of a common toxin from different pyogenic organisms under my case of Cellulitis recorded above.

Leask (Ibid June 20, 1896) used the serum in a case of puerperal fever and says the effect was "all for good". No bacteriological examination is mentioned.

Gaulard (Presse Médicale Nov. 1895) reports

two cases - one recovered and one was fatal. No bacteriological examination was reported and if this was not done, in neither case was the use of the serum justifiable; for in the first case the vigorous local treatment may have been the cause of the recovery, while the fatal case may not be in any way evidence against the value of the serum as it may have been not a streptococcic case at all or may have been a complicated case as Haultain's cases were respectively. The wholesale use of the serum in any or every case of puerperal fever is useless and unscientific and is only likely to cast undeserved reproach on its value.

Vinay (Lyon Médicale 1896) gives cases and emphasises the necessity of bacteriological diagnosis and early injection of serum and that the only objection to culture diagnosis is the inevitable loss of twenty-four hours. But as the serum is known to be harmless and as most cases of puerperal fever are probably due to streptococci there can be little objection to immediate injection and as soon thereafter as possible making a culture in order to give the

serum its right place in the treatment.

T. C. (Brit. Med. Jour. July 25, 1896) seems to take it as a surprise that he used the serum in one case with no improvement. He made no bacteriological examination so far as his report lets us know, so probably if he had ~~not~~ done so, he would not have expressed his surprise.

McKerron (Ibid Oct. 10, 1896) records three cases, one fatal, with no record of a bacteriological examination in any of them. He says that in all cases in which the serum has been tried whether with or without success it is important that the results should be put on record in order that the true value and position of the serum as a therapeutic agent may be early established. But this is not enough and would never enable us to attain to this object. If cases are treated without bacteriological aid in a perfectly empirical manner we will never get any nearer judging of its true value. As the serum is a product of bacteriology its value must be recognised only from a bacteriological point of view in its clinical use. It would be as sensible to give evidence

against the use of any drug in the Pharmacopeia because it is found to be useless in some disease it was never meant to and could never be expected to benefit as to give evidence against the antistreptococcus serum because it cannot benefit a puerperal fever which is in reality a true diphtheritic one, As already hinted the only thing that can excuse the use of the serum apart from bacteriological diagnosis is the fact that streptococci are probably the commonest of all the causes of puerperal fever and that culture diagnosis involves the loss of valuable time.

Williams (Ibid Oct.31, 1896) records six cases in only one of which an examination was made.

Adam (Ibid. Dec.26, 1896) records a case complicated by enteric fever in which the want of a bacteriological examination he owns prevented him from drawing any conclusions as to the effect of the serum.

Davies (Ibid. Dec.19, 1896) records one fatal case - no examination was made.

Moorhead (Ibid. Jan.23, 1897) records a case

in Cotehill Union Infirmary which recovered. No bacteriological examination was made but there is a strong presumption in favour of its having been a purely streptococcic infection as he had been attending a case of cellulitis of the leg at the time he attended the confinement, so that we cannot be surprised at the excellent result of the serum treatment in this case even in the absence of the definite grounds that a bacteriological examination would have given us.

Cummins (Ibid. Feb.13, 1897) records a case similar. He regarded it as certainly fatal had not the serum been used. It was a streptococcic infection as shewn by the erysipelatous rash which quickly disappeared after injection of the serum.

Sharp (Ibid. Feb.27, 1897) said the serum did good in his case though a bacteriological examination of the blood made was negative, while no examination was made of the discharge. But why in any case where there is a discharge ready at hand should anyone prefer to examine the blood for streptococci?

Fowler (Edin. Med. Jour. 1897) says that in

his case no examination was made but he judged the serum improved the rate and character of the pulse, caused reappearance of the lochia, and kept up the general well-being of the mother.

These cases without examination along with those of Coombes (Brit. Med. Jour. Feb. 1897) which was fatal and Mapleton (ibid. Ap.24, 1897) which recovered stand in contrast to those of Reddy and Edmunds which follow and in which an examination was made.

Reddy (Canada Med. Record. Sep. 1896) examination revealed streptococci and the case recovered.

Edmunds (Amer. Jour. of Med. Sc. Ap. 1897) examination shewed the case to be a genuine streptococcic one. No other surgical treatment was adopted. Thus two common fallacies were avoided which prevent us making a due estimate of its value, viz; absence of bacteriological diagnosis and treatment other than serum - therapeutic over and above the serum. The case recovered.

An extremely interesting case and instructive is that recorded by Norris (Amer. Obstet. Jour. Mar.

(1897). It was a true streptococcic infection, as evidenced by erysipelatous patches on the genital tract and later by an eruption of ~~the~~ facial erysipelas. It was extremely grave but the serum reduced the temperature from 105 to the normal and the pulse from 144 to 96 in twenty-four hours. Bacteriological examination of the facial erysipelas was negative and there was none made from the genital patches but the case is a strong argument in favour of the true germicidal qualities of the serum.

General Conclusions:-

That it is in purely streptococcic infections particularly in cellulitis and puerperal fever that at present this serum finds its greatest value - how far a still better result will be yielded by specially prepared serums for each distinct species of streptococcus, remains yet to be seen.

That it is ⁱⁿ incipient streptococcic inflammation that by far the greatest, if not the whole benefit of the serum is recognisable, and in this ^{sense} ~~case~~ its main field of usefulness is as a prophylactic

rather than as a curative agent and it therefore behoves us to use it as early in a case as possible.

That in every case a careful bacteriological diagnosis is eminently desirable.

That precedent to such the employment of the serum is justifiable only where there is a strong suspicion of the streptococcic nature of the affection, and with a view to saving time - but that even in these cases a bacteriological examination ought to be made as early thereafter as possible in order to corroborate the provisional diagnosis and so place the serum on a more stable and more strictly scientific basis as regards each particular case.

That in mixed affections its usefulness probably depends on the relation between the streptococci and the other organisms inasmuch as they or the other organisms may be the more virulent or in greater numbers, thus constituting the main cause of the affection.

That taking into consideration the published cases and the experiments of bacteriologists it seems

likely that the serums in use at present are anti-microbic and very slightly, if at all, antitoxic; and that all things point to the probability of a truly antitoxic serum being of wider application and usefulness than at present the anti-microbic serum is.