SOME REMARKS ON THE THERAPEUTIC VALUE OF ANTISTREPTOCOCCIC SERUM,

BY

MATTHEW BURROW RAY, MB., C.M., ('93)

Sefton House,
Harrogate.
Yorkshire
SYNOPSIS.

Page.

1  A few notes on the bacteriology of Septicaemia.

6  The writer's case of Enteric Fever with Streptococcic super-infection treated with Antistreptococcic serum. Recovery

24  Commentary on the above case.

30  A brief digest of current opinions as to the principles underlying the application of Antistreptococcic serum with a short account of its preparation.

38  Notes of Cases from various sources as illustrative examples.

53  Views as to the use of the serum in Puerpural Fever, Erysipelas, wound infection, Scarlet Fever, Malignant endocarditis etc. with illustrative Cases.

70  General Conclusions.

73  Bibliography.
The limitations of our knowledge of the pathology and etiology of Septicaemia, are accurately defined by Osler when he states:

(1) "that it is a term applied to any condition in which, either with or without a local site of infection, there is microbic invasion of the blood and tissues, but without metastatic foci of suppuration".

It will be noted that the above definition does not specify any particular micro-organism, neither is the necessity for a local site of invasion insisted upon.

The streptococcus pyogenes has generally been credited as an important factor in its causation, but we are still far from thoroughly understanding the true nature of the part it plays.

Many infections, at one time considered due to this pyrogenetic organism alone, are now known to be examples of a mixed infection, as for instance:

Diphtheria, which before its relationship to the Klebs-Loeffler bacillus was established by Loeffler and Klein, was thought by Oertal and others to be caused by the streptococci found in the false

(1).
membrane.

These cocci are also described as being important etiological factors in the production of such general diseases as Scarlet Fever, Small-pox and Puerpural Fever and also of local skin affections of an inflammatory nature together with superficial pus formation.

Other organisms have frequently been described as producing, or at any rate being associated in large numbers with, the septicemic state. These cases are usually very acute and correspond more nearly with the disease artificially induced in the lower animals such as mice and rabbits. (2)

The present impossibility of describing morphological differences, between the cocci found in a simple abscess and those associated with some acute disease such as say Puerpural fever, has led Woodhead and others to describe the following forms having different functional activities (3)

1. Streptococcus pyogenes,
2. Streptococcus pyogenes oedematous (Flugge),
3. Streptococcus septicus,
4. Streptococcus erysipelatus,
5. Streptococcus Septico-pyæmicus,
6. Streptococcus Articularum,
The first three forms prove rapidly fatal to mice and rabbits when injected into the veins. The next two are not so fatal in action; and the last is usually associated with septic changes in joints.

In 1895 Prof. Marmorek read a paper before the Societe de Biologie of Paris, in which he announced that he had successfully increased the virulence of certain forms of Streptococci so that, when injected into rabbits death ensued.

(4) A year later, Prof. Sims Woodhead gave the following terse summary of the researches in this direction:-

"1. That the streptococcus pyogenes must itself undergo great modification as regards its power of growing and of forming its special pus or inflammation producing products.

2. That it is so frequently found associated with other organisms in widely different conditions that the modifications mentioned may be well due in part to its symbiotic existence.

3. That it produces even when present in pus, say as a pure culture, such different degrees of reaction when inoculated into different species of animals in various states of health, that the state
of the tissues themselves must play a most important part in determining the life history and functional activity of the parasitic organism.

Referring to its two modes of life parasitic and saprophytic he further states—

"During its parasitic existence it is fighting against the surrounding tissue for its life and much of its energy may be expended in producing substances that will exert a paralysing effect on the living tissue. In other words when living at a higher level it does not reproduce itself nearly so rapidly as when in a saprophytic state and it is only as the higher or toxinforming functions become lessened that it is able to rapidly reproduce itself."

Unless it is decided that by the term septico-mia, we mean not one but a group of diseases, we must conclude that the many manifestations of this condition are due to a great variation in the virulence of the cocci.

It has already been stated that a recognisable site of invasion is not now considered an essential characteristic of the infection. Cases of general
infection may arise either in previously healthy patients or in the course of some other acute or chronic disease. Osler refers to 21 cases of this nature of which 13 were due to the streptococcus pyogenes, 2 to the staphylococcus and 6 to the pneumo-coccus. In 19 of these cases the patients were already the subjects of some other disease which was aggravated and in some instances terminated by the general Septicæmia. (5)

The term 'Cryptogenetic Septicæmia' has been suggested by Leube and others inasmuch as neither before nor after death is a local site of invasion discoverable. (6)

It therefore follows that the recognition of an infection is not by any means always an easy matter, and the importance of a bacteriological examination can hardly be under-estimated.

The notes of the following case, that occurred in my own practice, and which I had under observation for fourteen weeks, serve, not only as an example of this variety of infection, but also as an introduction to some remarks on the value of Antistreptococcic serum. (5)
The patient, a builder and contractor, married, aged 51, was seen on September 19th, 1902.

He complained of feeling run down, loss of appetite, bad taste in the mouth in the morning. Some headache at times. Itching and discomfort about anus, found later to be due to inflamed external haemorrhoids. The symptoms had commenced very gradually three or four weeks previously.

There was nothing of importance to note in his family history. His mother was still alive aged 89 and his children six in number all healthy. He himself led an active busy life with plenty of out-door exercise. His home surroundings, so far as could be ascertained, were perfectly hygienic. He was a non smoker and a total abstainer. No history of any serious illness. He stated that some years ago he experienced a little difficulty in passing urine, but for the last two years had not been troubled in this way. No history of any venereal disease could be obtained.

The first morning he was seen, his temperature was found to be 101°. The lips and chin showed (6).
considerable pallor compared with the rest of the face, which had a somewhat dusky hue. The hands and nails exhibited nothing abnormal. No glandular or other enlargements of like nature present.

The appetite was very poor and he had at times great nausea and distaste for food. He was greatly troubled with flatulence and a feeling of distension. The bowels were very variable, though as a rule inclined to constipation.

Teeth practically absent. He had a false set for upper and lower jaw. The middle and posterior parts of the tongue were coated with white fur. The sides red and inflamed. There was also some slight ulceration posteriorly.

The abdomen showed on inspection a slight amount of uniform distension due to flatus.

No increase in hepatic or splenic dullness.

He complained of a little cough at times especially in the early morning with a little colourless frothy expectoration. Dypsnoea was experienced on slight exertion but no particular pain. Examination of the chest anteriorly revealed nothing abnormal. Posteriorly on the (7).
right side the percussion note was a little impaired and occasionally a few fine crepitations could be heard towards the end of inspiration.

As regards the circulatory system, beyond the dyspnoea referred to above, he had nothing to complain of. The pulse was 80 to 90 regular and of moderate tension. No thickening of the arterial walls. The apex beat was normal in position and the superficial and deep cardiac dullnesses were not increased. The sounds were heard clearly in the different areas and in the aortic there appeared to be slight accentuation of the second sound.

The urine was scanty and highly coloured and of a high specific gravity. A deposit of urates on cooling.

An examination of his other systems showed nothing abnormal.

The following is a short account of the subsequent progress of the case. Negative details have as far as possible been omitted.
Temperature Charts of case under writer's care.

2nd Week:

<table>
<thead>
<tr>
<th>Date</th>
<th>09/27</th>
<th>09/28</th>
<th>09/29</th>
<th>09/30</th>
<th>10/01</th>
<th>10/02</th>
<th>10/03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>102</td>
<td>103</td>
<td>104</td>
<td>105</td>
<td>106</td>
<td>107</td>
<td>108</td>
</tr>
</tbody>
</table>

No regular chart during 1st week of observation.

3rd Week:

<table>
<thead>
<tr>
<th>Date</th>
<th>10/03</th>
<th>10/04</th>
<th>10/05</th>
<th>10/06</th>
<th>10/07</th>
<th>10/08</th>
<th>10/09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>102</td>
<td>103</td>
<td>104</td>
<td>105</td>
<td>106</td>
<td>107</td>
<td>108</td>
</tr>
</tbody>
</table>

4th Week:

<table>
<thead>
<tr>
<th>Date</th>
<th>10/10</th>
<th>10/11</th>
<th>10/12</th>
<th>10/13</th>
<th>10/14</th>
<th>10/15</th>
<th>10/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>102</td>
<td>103</td>
<td>104</td>
<td>105</td>
<td>106</td>
<td>107</td>
<td>108</td>
</tr>
</tbody>
</table>

5th Week:

<table>
<thead>
<tr>
<th>Date</th>
<th>10/17</th>
<th>10/18</th>
<th>10/19</th>
<th>10/20</th>
<th>10/21</th>
<th>10/22</th>
<th>10/23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>102</td>
<td>103</td>
<td>104</td>
<td>105</td>
<td>106</td>
<td>107</td>
<td>108</td>
</tr>
</tbody>
</table>

6th Week:

<table>
<thead>
<tr>
<th>Date</th>
<th>10/24</th>
<th>10/25</th>
<th>10/26</th>
<th>10/27</th>
<th>10/28</th>
<th>10/29</th>
<th>10/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>102</td>
<td>103</td>
<td>104</td>
<td>105</td>
<td>106</td>
<td>107</td>
<td>108</td>
</tr>
</tbody>
</table>
Temperature Charts of case under writer's Care.

### 7th Week

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct. 31</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 1</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 2</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 3</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 4</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 5</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 6</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 7</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 8</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 9</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 10</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 11</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 12</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 13</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 14</td>
<td>AEEEEE</td>
</tr>
</tbody>
</table>

### 8th Week

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 15</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 16</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 17</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 18</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 19</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 20</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 21</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 22</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 23</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 24</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 25</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 26</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 27</td>
<td>AEEEEE</td>
</tr>
</tbody>
</table>

### 9th Week

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 28</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 29</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Nov. 30</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 1</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 2</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 3</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 4</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 5</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 6</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 7</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 8</td>
<td>AEEEEE</td>
</tr>
</tbody>
</table>

### 10th Week

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 9</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 10</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 11</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 12</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 13</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 14</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 15</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 16</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 17</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 18</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 19</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 20</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 21</td>
<td>AEEEEE</td>
</tr>
</tbody>
</table>

### 11th Week

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 22</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 23</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 24</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 25</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 26</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 27</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 28</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 29</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Dec. 30</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 1</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 2</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 3</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 4</td>
<td>AEEEEE</td>
</tr>
</tbody>
</table>

### 12th Week

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan. 5</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 6</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 7</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 8</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 9</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 10</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 11</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 12</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 13</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 14</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 15</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 16</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 17</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 18</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 19</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 20</td>
<td>AEEEEE</td>
</tr>
<tr>
<td>Jan. 21</td>
<td>AEEEEE</td>
</tr>
</tbody>
</table>

(10)
Temperature Chart of case under writer's care.

<table>
<thead>
<tr>
<th>13th Week</th>
<th>14th Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>20th</td>
</tr>
<tr>
<td>Days</td>
<td>20-12</td>
</tr>
<tr>
<td>Time</td>
<td>9:00 AM</td>
</tr>
<tr>
<td>Temperature</td>
<td>MEME</td>
</tr>
</tbody>
</table>

(11)
FIRST WEEK.

During the first few days he had several attacks of nausea and vomiting for which an effervescent mixture was prescribed with good results. The temperature varied between 102° in the morning and 104° in the evening. Each rise of temperature was marked by a rigor, lasting in some cases, for three quarters of an hour. The pulse was regular; averaging 80 to 100 per minute. The respirations 18 to 22. The dulness at the base of the right lung became more pronounced and some impairment of the percussion note on the left side was also noted. On auscultating over these areas, a number of fine and medium crepitatious were heard towards the end of inspiration. The abdomen became more distended but no rash appeared as yet. The hepatic and splenic dullness showed no increase. The bowels were constipated and several enemas had to be administered. Flatus was passed very freely. The inflamed state of the haemorrhoids caused much uneasiness, to relieve which he was ordered hot fomentations and Ung: Resinol. He slept fairly well and took nourishment, chiefly consisting of (12).
milk, very freely after the nausea had subsided.

He remained in bed practically all the time.

A systematic record of the temperature was not kept during this week.

2nd Week.

The temperature, which was now regularly charted, shows a considerable diurnal variation. He lay on his back in bed, as a rule, although at times he managed to keep on one or other side for half an hour or more. The rigors were more marked and usually ushered in by great pallor of the lips and chin and bluness of the rest of the face. They were treated by wrapping the patient in blankets and applying hot bottles to feet and sides. The cardiac condition and pulse continued in much the same state. The respirations were not markedly increased and dypsaæawas not complained of to any extent. The dulness at the pulmonary bases became a little more pronounced. A few rose spots made their appearance over chest and abdomen; they however soon disappeared and were not replaced. The distension of the abdomen and splenic and hepatic dullness remained (13).
the same. The bowels were still constipated and the faeces pale, slimy and offensive. The inflamed haemorrhoids soon subsided under treatment. He commenced to have difficulty in passing urine and in a few days had complete retention. This was relieved by a catheter. He was ordered Urotropin in Seltzer water twice daily which had the effect of greatly clearing the urine. He as a rule obtained five or six hours sleep each night but was at times a little delerious. During the day he was remarkably clear and bright. He continued to take milk very well. Stimulents were ordered very sparingly and only when he appeared at all collapsed after a severe rigor.

3rd Week.

The morning and evening temperatures now showed if anything a greater variation; an evening rise of 106°F being on one occasion recorded. The retention of urine continued, requiring the use of the catheter three times during the twenty-four hours. The bowels rarely acted without an injection and the motions were much as above noted. He passed fairly
good nights and took his nourishment very well.

October 4th, 1902. He was this day seen in consultation with Dr. Barr and his condition found to be as follows.- He was lying on his back and fully able to answer questions, displaying great anxiety as to the nature of his illness. The tongue was coated in streaks and very dry at the edges. The abdomen was markedly distended and tympanitic. No rose spots to be seen. The liver dullness slightly increased below the costal margin. The spleen also showed signs of enlargement. Examination of the heart revealed nothing that was not easily accounted for by his weak state. The pulse was rapid 90 to 100 and of moderate tension. The dullness at the pulmonary bases and the auscultatory signs were decided to be due chiefly to hypostatic congestion. The respirations were not unduly hurried. The urine gave Ehrlich's diazo reaction in a well marked manner. A sample of blood gave a positive result later with the agglutination test. A definite diagnosis of Enteric Fever was therefore made based on the general condition of the patient and the observations recorded above.

As regards treatment he was ordered to be kept on a milk diet varied by whey and a little syrup of (15).
glucose. Internally a mixture containing Beuzo- Naphthol, Calci Chlorid:, Elixir Saccharin:, and mist: Amagydal: was prescribed and a ten grain powder of Sulphate of Quinine to be given daily two hours before the rigor generally appeared, The lower bowel was ordered to be washed out daily by a gravitation douche containing a solution of Potass: Permang:

4th Week.

For the first day or two the temperature did not fluctuate quite so much; but later in the week it reached 104° and over. He was often very collapsed after the rigors which continued to usher in rises of temperature. He was generally given brandy and champagne or hot milk or beef tea as restoratives. It was often observed that quite as much benefit was obtained from the latter as from alcoholic drinks. The Quinine was discontinued as it somehow seemed to cause an increased amount of blueness and to aggravate the general depression. The tongue remained much the same. There was no change in the character of the pulse (16).
There was no increase in the number of the res-
pirations and no particular pain or discomfort was
complained of in this connection. The cough was
slight and a little rusty-coloured sputum accom-
panied it. The abdomen was still much distended
and both hepatic and splenic dullness enlarged.
The bowels usually acted only after the rectal
douche or enema. The urine continued to require
the catheter and the effect of the Urotropin was
decidedly beneficial.

He took an average four pints of milk in the
twenty-four hours, and sometimes more, in addition
to the whey and glucose. He obtained plenty of
sleep, a very important factor.

5th Week.

Throughout his illness he perspired very freely
after each rise of temperature and especially
through the night.

His condition remained much the same in every
way except that the constant use of the catheter
was beginning to cause a little pain and uneasiness.
The meatus appeared a little swollen and irritated.

He still contrived to get a fair amount of
sleep, as a rule five or six hours each night and
(17).
perhaps an hour or two in the day. His mental faculties showed no deterioration. He was also able to take the usual quantity of nourishment.

6th Week.

The oscillation of temperature was greater. A fall to below 96° being charted; it was however counterbalanced on the following day by a rise to nearly 104°. The condition at the meatus resolved itself into a slight urethritis with blueing together of the lips. Considerable difficulty was experienced on one or two occasions in passing the instrument. Fortunately however he was beginning to show signs of a diminution of the retention because he once or twice succeeded in emptying the bladder in a natural manner. He complained of a little pain in the groins, but on examination no glandular enlargement could be detected. The abdominal symptoms were much the same. The tongue still dry and coated. The cough troublesome at times and the sputum tenaceous and thick but clearer than before; no increase of dullness posteriorly. The strength of the heart and pulse continued to be well maintained.
He slept well and showed no particular distaste for food.

7th Week.

The temperature on the whole showed some improvement. For three days there being practically no rise. He gradually regained full control over his bladder and by the end of the week the catheter no longer required to be used. The urethritis chiefly confined to the penile portion persisted, and pus was present in the urine but only in small quantities. There was no evidence of any extensive Cystitis. The condition of the lungs posteriorly showed as slight improvement, but the cough was more troublesome; the sputum clearer but more tenacious. Beyond this there was no other change of importance to record.

8th Week.

For four consecutive days there was no rise of temperature during which interval he distinctly gained in strength. The dullness posteriorly continued slowly to show signs of resolution and the (19).
breath sounds were much clearer. The abdomen remained very distended and the enlargement of both liver and spleen greater than when last noted. The bowels were if anything a little less constipated and flatus was passed very freely. The urethritis gradually disappeared as did also the pus from the urine. It was noticed that he had lost flesh considerably but did not perhaps show quite the emaciation that might have been expected.

At the 9th Week.

At the beginning of the week the temperature showed signs of improvement but by the end it was in much the same state as before. The urine was now clear and passed in a perfectly natural manner. The bowels were less constipated and the motions quickly acquiring a more normal appearance. He suddenly developed great pain running up the left thigh with some oedema about the lower third of the leg and ankle. Thrombosis was feared but the application of a few fomentations of Tr: opii soon relieved the pain and the swelling soon almost disappeared. For the first time the pulse was occasionally noticed to be dichrotic but never for very long together.

(20).
He continued to sleep and take nourishment very well.
His mental faculties remained very acute.

10th Week.

Although absolutely no local cause could be assigned, he had a series of very severe rigors followed by hyperpyrexia, the temperature on one occasion nearly reaching 107°. During this particular attack the pulse could not be counted and the respirations were 45 to 50 to the minute. Cold affusions were at once applied to chest and abdomen and whisky given internally. The temperature fell to 103° in twenty minutes and the respirations to 30 the pulse slowing down to 110. After a further fall in temperature to 101° he had early the following morning a similar attack but on this occasion 107° was actually reached. These seizures left him in a very exhausted condition although he still took his food very well and obtained a fair amount of sleep in the intervals.

As regards his other symptoms, they remained very much in the same state as when last noted.
11th Week.

On November 28th 1902, he was again seen in consultation with Dr Barr and on examination his state was briefly as follows:

The tongue anteriorly was red and inflamed, posteriorly coated with yellow fur. The pulse was 90, regular but wanting in force. The heart showed little or no sign of dilatation, both sounds being clear and distinct. The dullness at the pulmonary bases had cleared considerably and comparatively few accompaniments were to be heard on auscultation. The cough was a little troublesome but the sputum quite clear but tenaceous. The distention of the abdomen was not so marked although the splenic and hepatic dullness still showed signs of increase. The urine was a little albuminous. At a later examination Streptococci were demonstrated in the blood and faeces.

He was ordered a mixture containing Salol, Calcii Chlorid:, Quin: Salicyl:, Syrup of orange, and Mist: Aucagyd:. It was also decided to try the effect of repeated injections of Antistreptococcic Serum. 20C. CM. were accordingly given at once and 10C. CM. (22).
every succeeding day for 14 days. This was carried out and by the end of the week marked improvement was noticed in the temperature.

12th Week.

The serum injections, which were given in alternate flanks, were continued throughout the week and the temperature never rose above 101°, but showed a gradual decline. The rash, usually associated with the use of the serum, was never well marked.

His general condition rapidly improved. The distention of the abdomen with the accompanying enlargements of liver and spleen soon subsided.

The tongue was soon clean and moist. The pulse slowed down to 70 or 80 and increased in force. The dullness posteriorly cleared greatly. A limbus was ordered for the cough which at times was very troublesome. He was soon able to sit up in bed unaided. A greater variety in the way of food was allowed of which he partook heartily.

13th Week.

The serum was discontinued and the temperature,
with but a slight exception, was subnormal throughout the week. He continued to make uninterrupted progress towards recovery. The cough gradually ceased and the remaining dullness to clear. He sat up most of the day and walked about the room.

14th Week.

Temperature subnormal and by the end of the week patient was convalescent and able to go out each day for a drive or short walk.

The earlier diagnosis of Enteric Fever was founded not on clinical observation alone but on the result of the agglutination test, which in Cabat’s collection of 5978 cases gave a positive reaction in 97.2 per cent. Ehrlich’s diazo reaction, which was also well marked, is valuable in confirming the diagnosis.

Enteric Fever at the age of 51 is not by any means common. Osler mentions that out of 829 cases, (24).
with but a slight exception, was subnormal throughout the week. He continued to make uninterrupted progress towards recovery. The cough gradually ceased and the remaining dullness to clear. He sat up most of the day and walked about the room.

14th Week.

Temperature subnormal and by the end of the week patient was convalescent and able to go out each day for a drive or short walk.

The earlier diagnosis of Enteric Fever was founded not on clinical observation alone but on the result (7) of the agglutination test, which in Cabot's collection of 5978 cases gave a positive reaction in 97.2 per cent. Ehrlich's diazo reaction, which was also well marked, is valuable in confirming the diagnosis.

Enteric Fever at the age of 51 is not by any means common. Osler mentions that out of 829 cases, (5)
treated at John Hopkins Hospital, only six were between 50 and 60 years of age.

As regards the presence of a later or super-infection, a brief review of some of the clinical and other features of the case will prove of considerable assistance in arriving at a definite conclusion on this point.

In uncomplicated cases convalescence is usually well established by the sixth or at latest the seventh week. Murrell\(^{(a)}\) however relates an instance of one, that occurred at the Westminster Hospital, where, without any relapses, three months elapsed before complete defevergence. It was not considered to be of the nature of post typhoid pyrexia because the diarrhoea and typical stools persisted to the end. Cases lasting eight or nine weeks are not very rare and have probably been met with in the experience of most observers. They do not as a rule exhibit such marked variations of temperature in their later stages.

The chills constituted one of the most noticeable clinical features in the case under consideration. At times the rigors were almost convulsive in their
severity, lasting often from an hour to two hours or more. Practically every well marked rise in temperature was so ushered in. The elevation was never long maintained as profuse perspiration and cold sponging or affusions generally induced a speedy fall. If this had not occurred a fatal termination from hyperpyrexia might easily have ensued on than one occasion. On examining the accompanying charts it will be at once seen that the diurnal rise and fall is much greater than in ordinary instances. Neither is it common to find such great elevations during the last stages.

Bosanquet in an analysis of 215 cases of Enteric finds that in two only was a temperature of 106° attained and both proved fatal.

In Osler's analysis of the 829 cases before referred to 33 reached a height of 106°. In this particular case a record of 107° was on two occasions charted.

In the earlier weeks this great oscillation did not call for much remark; but when a rise of a 107° is recorded at the end of the tenth week a further explanation is naturally looked for.
Some local cause at once suggests itself and the influence of the urethritis is the first to be considered. This urethritis undoubtedly arose in the first instance from the constant use of the catheter to relieve the retention, which commenced during the second week of observation and lasted about five weeks. He first experienced discomfort about the third week of its use. A fortnight later the catheter was discontinued and for a few days he had a free discharge of pus from the urethia. As far as could be ascertained it was chiefly the penile portion that was acutely inflamed although the prostatic portion would also be to some extent involved. He never had any glandular enlargement or abscess formation as a result. By the time the period of hyperpyrexia recommenced, that is the tenth week, the urine was practically clear and he had, between the subsidence of the urethral symptoms and the period above mentioned, a subnormal temperature for four days. It must also be noted that he had in the third week of his illness, before any urethral trouble occurred, on one occasion a temperature of 106°F. From these facts it will be easily seen that further evidence should therefore be searched for.
The dullness and other signs at the pulmonary bases were always regarded as due purely to hypostatic congestion. Real pneumonic symptoms were never present. The breathing was only hurried when the temperature rose and he never complained to any extent of pain or dyspneæa. Here again a marked improvement had taken place before the state of his temperature assumed such alarming proportions.

It will be noticed that constipation persisted throughout. This is by no means uncommon. It occurred in one sixth of Bosanquet's series of 215 cases. Osler mentioned diarrhoeæa as occurring in 20 to 30 per cent of his cases and further points out that its absence must not be taken as an indication that the intestinal lesions are slight. Fortunately in this instance the precise extent of bowel involved was never accurately determined.

In ordinary cases it is quite common to find a very extensive area of ulceration and the terminal 6 or 8 inches of the ileum may according to the above observer form one large ulcer. It is therefore quite conceivable that from such a raw surface an extensive invasion of the blood and tissues by bacteria might ensue. Streptococci were demonstrated (28).
in both blood and foeces; and the almost magical action of the Antistreptococcic serum is, as will be seen later, one of the best possible proofs of the part that these particular organisms were playing.

The infection, judging by the temperature chart, probably commenced early in the course of the disease, and for a portion of the time, the two infections, Typhoid and Septicaemic were at work together; but as the one declined, the other gained in virulence.
The beneficial effect following the use of the serum is one of the most striking features in the history of the case. It can hardly be disputed that it is to this remedy that he owes his recovery. Beyond a little soreness after each injection no ill effects were experienced during its exhibition. As I remarked before the urticaria often described in this connection was never well marked. Considering the duration of the illness the improvement was rapid and he recovered his strength in a very remarkable manner.

Since its introduction in 1895, ANTISTREPTOCOCCIC serum has received a very extended trial and the results attending some of these trials are certainly not so uniformly successful as those following the use of Diphtheria antitoxin. Whatever may be urged to the contrary it certainly has in many instances a marvellous effect. Before entering into a fuller discussion on its value I shall endeavour to elucidate the main principles underlying its successful application by means of the following brief digest of the current opinions.
regarding recent investigations in this direction.-

Serumtherapy, is based on the observation that immunity, or resistance to any given poison or infection, may be natural or artificially acquired.

There are, practically speaking, two views as to how this resistance may be acquired; the one biological, and the other chemical, supported respectively by Metchnikoff and Ehrlich. Later researches have shown that these theories are, fundamentally speaking, not so much opposed to each other as they were originally considered to be, or as Grunbaum puts it "they are really only rays refracted at different angles from the same source of light and will be ultimately be made to fuse into one brilliant cellulo-humoral theory of immunity".

The biological school believe that the body is protected from invasion by the activity of the white cells which seize upon and dispose of bacterial invaders.

Ehrlich and his followers regard a bacterical toxin as poisonous only in the form of a chemical combination with some constituent of the cell.
Those cells which do not possess this particular constituent which unites chemically with the toxin, are termed immune. Certain anomalous results arising in Ehrlich's investigation for the standardization of diphtheria toxin led him to assume and afterwards to prove, that in certain circumstances the toxin might be modified into a toxoid which was nearly non poisonous, but was nevertheless capable of uniting with the antitoxin. These toxoids were further subdivided as follows according to their affinity for the antitoxin.—

1. Protoxoid having greater affinity than the toxin
2. Syntoxoid " equal " to the toxin
3. Epitoxid " less " than " "

Further researches in this direction led to the enunciation of the famous side chain theory.

The side chains are likened by chemists to radicles, more or less complex, attached loosely to a nucleus of closely welded atoms known as the proteid molecule. This molecule is probably capable of great variation in its structure and nature; this variation depending on the union or otherwise of the side chains of one molecule with side chains, either free or attached, of another.

(32).
The following example quoted by Bokenham will perhaps elucidate this point

"Belladonna can be eaten with impunity by goats, although to most other animals it acts as a poison. Goats are therefore immune because there are no side chains in their molecules to unite with the side chains of the belladonna molecule!"

As a consequence of the combination of a given toxin with certain side chains, the composition of the molecule to which they belong will tend to be affected and this embarrassment will stimulate metabolism to replace these altered side chains; or in Ehrlich's own words:-

(18) "In the course of a typical process of immunization the cell becomes trained, so as to speak, to produce the specific side chains in large quantity. In such a process of regeneration not compensation but hyper-compensation is the rule and with the enormous increase of the poison dose a point must be reached when there is such an excess of side chains, that the cell is surfeited and casts them off as useless balast into the blood. If on the one
hand the presence of such receptive side chains is a necessary condition for the occurrence of the toxic process, this circumstance also explains in the most simple way the production of the antidotes.

In other words these liberated side chains retain their ability to unite with the corresponding poison in any situation in which they happen to come and are ANTITOXIN.

These side chains are specific and remain so, ie they can only unite with corresponding structures or poisons.

If a susceptible animal be inoculated with increasing doses of a given poison a condition of tolerance is set up. This condition is described by Ehrlich as "active immunity" because it causes the formation of specific side-chains which are able to neutralise further doses of the same poison. These side chains perist in the serum and retain all their characters. If some of the serum be introduced into a fresh animal a condition of "passive immunity" proportional to the amount introduced is set up and passes off as the antitoxin is eliminated.
Anti-toxin immunity must be distinguished from immunity to infection; there are therefore two kinds of curative serum. Antitoxins which neutralise the bacterial toxins and thus indirectly annul the effect of living bacteria eg. diphtheria.

Antibacterial which prevent the invasion of the body with living bacteria eg. Anti-Streptococcic serum.

The following is a brief note on the preparation of this serum.

(19) The serum is obtained from the horse or donkey after subjecting the animal to repeated injections of living virulent streptococci.

As an ordinary cultivation of streptococci is quite useless for this purpose the increased amount of virulence required is obtained by the repeated passage of the organism through rabbits and also by cultivating the growths on peptonised bouillon containing 2°/o glucose.

(20) The susceptibility of different horses varies greatly but as they show less constitutional disturbance than donkeys, they are now usually employed for this purpose. At first a small dose of from 1 to 2 C CM is injected into the sub-cutaneous
tissue of the shoulder. After recovery from the swelling, pyrexia and malaise, a second injection of a larger amount is made; and when this has recovered another is made and so on, repeating the injections for several months the dose being increased on each occasion.

The animal is then bled and the serum allowed to separate; after which it is filtered through a porcelain filter under pressure in order to prevent the possible pressure of living Streptococci which are known to persist in the blood for some days after their introduction.

After standardising, the serum is ready for use and the best results are usually obtained when this is perfectly fresh or at any rate when not more than three or four weeks have elapsed.

(21). Bokenham and Professor Denys of Louvain seem to have almost simultaneously come to the conclusion that the only way of procuring better results with the serum was to immunise the animals destined to furnish it with as many strains of Streptococci as possible. In this manner they each obtained serums of far greater activity than could be obtained in the usual way. They therefore advocate the supply.
of a perfectly fresh polyvalent serum direct from the expert to the user.

On re-reading through the literature bearing on the use of Antistreptococcic serum it will at once be seen, that the majority of recorded cases are those in which a well recognised site of bacterial invasion is present and in many instances the indications for the employment of the serum is derived from clinical evidence alone. The following case has been selected on account of the nature of the primary affection Viz-. Enteric Fever. A well marked local manifestation of secondary invasion is present and it is therefore to be regarded as a commoner form of secondary Septicæmia.

The earlier diagnosis unfortunately does not seem to have been confirmed by the Agglutination test, although the diazo reaction gave a positive result which of course of itself is not regarded as sufficient. The weight of clinical evidence would however point to the assumption that the diagnosis is correct. Although the precise nature of the super-infect
was not demonstrated bacteriologically, the use of
the serum was in a high degree beneficial.

Leicester Infirmary,

(22). A case of Enteric Fever with severe periosteal
lesions. Injections of Antistreptococcic serum.-
recovery.

Under the case of Dr. Astley V. Clarke notes by
Mr. R. H. Fagge House Physician.

Boy aged 12 admitted to the Leicester Infirmary
suffering from Enteric Fever which was clinically
well marked.

Abdomen distended, rose spots present pain in
back and headache. The urine contained a trace of
Albumin and gave Ehrlich’s diazo reaction well.
The disease seemed to run a fairly normal course
until the 27th, day of the illness when pain and
swelling were noticed on the first phalanges of the
right ring finger. Two days later an incision was
made but no pus evacuated. Further incisions were
made in the course of the next few days but no

(38).
improvement occurred. About the 44th, day of the disease the finger was amputated and it was found that the whole of the periosteum was separated from the bone but the Meta-carpo-phalangeal joint was not affected.

He was very dull and apathetic mentally and he did not seem to understand anything said to him. Six days later neither mental or local condition had improved and an incision was made over the metacarpal bone. Later, five days, he was still unconscious with much delirium, temperature oscillating between 99° and 106°.

10 C. CM Antistreptococci serum were injected into left loin. Shortly afterwards temperature fell by crisis to normal, delirium vanished and consciousness returned within twenty-four hours. Injections of 5 C. CM were given on three succeeding days and patient rapidly got well, the hand improving after the first injection.

Unfortunately no cultures were obtained from the hand when it was first opened.

With regard to the case Dr. Astley Clarke says. "Periostitis is a well recognised complication of typhoid fever and two varieties seem to occur; in one the local lesion is caused by the typhoid..."
bacillus, but in the other it is the result of a secondary streptococcic infection. The improvement which followed the injection of antistreptococcic serum was very striking and if not due to a coincidence it is in favour of the view that the periostitis was the result of the presence of the strepococcus.

In the next instance the duration exceeds that of the case under my own care. This is chiefly due to the occurrence of a well marked relapse when convalescence was almost established. The respective ages are widely different and in my case the various complications such as perforation, peritonitis and parotid bubo are absent. Here again the Septicemia can be traced to a local cause. The primary diagnosis was confirmed, after repeated trials by the agglutination test. There does not however seem to be any record of a bacteriological investigation of the secondary infection. Considering the comparatively small amount of serum used 55 C
in all, the result of its application is highly satisfactory. and it would have been interesting to have seen the effect on the relapse by a continuation of the treatment.
Temperature Chart of case of Dr Hawkins and Mr Thurston.
Temperature Chart of case of Dr Hawkins and Mr Thurston.
A case of Typhoid Fever of unusual duration. (23).
Perforation of Cecum and peritonitis, Operation; Antistreptococcic serum used: Recovery.

Dr. Hawkins and Mr. Thurston,

St Thomas's Hospital.

The patient, a girl aged 11 years, was admitted into St. Thomas's Hospital on October 14, 1898. Five days previously she had shivering followed by heat and pains in the limbs; but she had been ailing for some days with diarrhoea and nocturnal delirium. At first the Agglutination test gave a negative reaction and the diazo-reaction doubtful. The abdomen was distended and the spleen could be felt. During the first five days after admission the temperature remained between 102° and 103° F. It then began to fall with a large daily variation but eight days later a fresh accession of fever set in. The bowels tended to constipation throughout, enemata being required from time to time. The temperature which sometimes reached 104° and 105° F showed a large daily oscillation. The spleen was considerably enlarged, the abdomen much distended and one doubtful rose-spot present.

Up to the 41st, day of the illness all
appearances were favourable when she was suddenly seized with sickness and pains in the abdomen. The pains quieted but recurred at intervals with increasing severity and 15 hours later the symptoms of perforation having become so urgent it was decided, after much difficulty in obtaining permission, to operate. The abdomen was opened and a perforation found on the anterior caecal wall. This was closed with a row of Lemberts sutures. The abdomen was irrigated, mopped out and the wound closed with silkworm gut sutures. It was not considered advisable to prolong the operation by a lengthy search for other ruptures.

Following this an attack of peritonitis occurred which lasted a few days but quickly cleared up and by the end of a week all anxiety on this score was at an end. A parotid bubo on the right side now made its appearance and an abscess developed in the buttock, at the site of a former injection of saline fluid. The abdominal wound gaped widely and showed no signs of repair. Thirteen days after the operation the wound was re-sutured and the bubo and abscess in the buttock opened. Six days later the patient complained of pain and tenderness in the right femur but no swelling could be found.
Two days later a double otitis media supervened. Three days later the pain in the thigh ceased but there was effusion into the left knee joint with pain and tenderness followed on the next day with a similar condition in the right knee.

ANTISTREPTOCOCCIC serum was now injected in a daily dose of five cubic centimeters for the next eleven days and during this period there was great improvement in the general and local conditions. The bubo and the abscess disappeared, the abdominal wound began to heal, the knee joints became normal, the discharge from the ears gradually ceased and the temperature fell to normal. The knee joint was probably of septic origin and was not an instance of the specific typhoid arthritis described by Keen. For the next 24 days the patient slowly improved and there was no ground for anxiety.

On January 12th, 1899, a definite relapse set in which lasted 14 days and for the first time Widals' test gave a positive reaction and the spleen again became enlarged. The abdomen was somewhat distended, the tongue was furred and the temperature at the height of the relapse reached to from 103° to 104°. On January 26th, the temperature again became normal and real convalescence began. The patient,
a year after the outset of the illness, was fat and well and presented no signs of abdominal disease.

(23) Commenting on the case the observers say:—
"apart from the saving of a life after the outset of general peritonitis due to perforation of the caecum this case of typhoid fever presents of interest.

The total duration of the case down to the cessation of the fever was 114 days. This period comprises an attack lasting 76 days, an interval of 24 days of slight irregular fever and a definite relapse lasting 14 days.

Widals test only gave a positive reaction on the one hundred and third day having been negative on the 15th, 22nd, and 37th, day of the disease.

When the patient fell into a septic state about a fortnight after the operation developing a parotid bubo and an affection of the knee joints, the abdominal wound showing no tendency to heal, the administration of 55 cubic centimeters in 11 daily doses may perhaps be credited with good effect."
Chart of Dr. Abercrombie's Case


(47)
Case of Septicaemia of Cerebro-Spinal Type. (24). Under care of Dr. Abercrombie

J. R. B. a clerk was admitted into Charing Cross Hospital on May 31st, 1898 for fever with delirium and drowsiness. The previous history was unimportant. He had been ill for 26 days. The first symptoms were a feeling of drowsiness which lasted for three days, then nocturnal restlessness, vomiting and the development of the phenomena which continued prominent throughout. These were:—fever ranging between normal and subnormal and 105° with occasional rigors, pains in the head and down the back and tenderness of the head, muscular spasm and a degree of opisthotonos and bouts of restlessness, insomnia and incoherence or active delirium.

The periods of remission each extending over one or two days, during which the boy both looked and felt well, were a striking feature of the case. The interruptions of this condition were sudden and characterised by rigors, rises in temperature, sickness, restlessness and incoherence.

The urine was found to be albuminous repeatedly. Epistaxis occurred on three occasions; on the 33rd, day of the illness a soft systolic murmer was heard over the cardiac apex.

(48).
On the thirtyninth day 10C. cm of Antistreptococcic serum were injected under the integuments of the abdomen. The temperature fell steadily but this proved to be only one of the ordinary periods of remission for although a second injection was given next day, the temperature rose again on the third day and two days later the patient was in much the same condition with a temperature of 105-2 vomiting and delirium severe headache and retraction of the head. Quinine was now tried (gr. v bis die) and the temperature fell as usual only to rise again to a 104° nearly.

On the forty-eighth day a second course of Antistreptococcic serum injections was commenced; six in number. the temperature never again reached 100° becoming practically normal and therewith the patient improved steadily. The cardiac murmurs continued audible for a few days and finally disappeared. The boy was finally discharged on the seventy-sixth day, perfectly well, having gained six pounds in the last sixteen days in Hospital.

Commenting on the case Dr. Mitchell Bruce says--
(24) 1. In some cases of a septic kind Antistreptococacic serum is successful.

2. That the effect may be extremely rapid.

3. That the success may be obtained after other measures has failed.

4. That success may be obtained with one serum after another serum has failed. There was no suggestion that the first serum was bad as it was derived from an unimpeachable source: It was regarded as simply different in some occult respect. One practical lesson from this case was not to be content with the trial of one serum if it prove unsuccessful.

In the following instance although the source of the infection was well known the diagnosis was confirmed bacteriologically. It is of interest on account of the acute character of the case and the absence of local symptoms.
Case of Acute Septicaemia heated by Antistreptococcic serum - Recovery

by

T.C. Coleman and T.G. Wakeling.

(25) Dr. - middle aged, attended fatal case of Puerpural Septicaemia and at once showed signs of poisoning. He had no local symptoms although it was stated he had an abrasion on the right forefinger. He commenced with acute dyspepsia and vomiting; complaining that he could not get rid of an awful smell.

15 days elapsed before he was seen when his temperature was found to be 104°. He was delirious at times. Had violent hiccough. A few crepitations at the base of right lung.

16th day. - Wildly delirious, temperature 104.6. Pulse 110. Respiration 50.

Signs of pneumonia well marked over right base. Diagnosis of Septicaemia made.

17th day. - Symptoms aggravated. Had retention of urine and catheter passed.

18th day. - Hiccough constant obstinate constipation.

Complexion very livid. Pulse 116 feeble and intermittent.

(51).
20 C. CM. ANTISTREPTOCOCCIC serum were injected followed two hours later by a second injection of 10 C. CM. Two hours later he was conscious for the first time for three days. Injection of 10 C. CM repeated every four hours.

19th, day.- Temperature down to 100.". Hiccough less troublesome. In the evening temperature reached 103.6. Injection reduced to 5C. CM every seven hours as supply was running short.

21st, day.- No serum since 19th, day patient much worse. 2½ hours later 5 C. CM serum given and he at once seemed better.

22nd. day.- Delirious at times and catheter still to be used.

23rd, day.- 10 C. CM of serum injected and owing to a difference of opinion discontinued until the

29th, day. and he gradually relapsed. Slight improvement followed a single injection when the serum was again discontinued until the

33rd, day.- and then recommenced; 10 C. CM being given twice a day. Immediate improvement (52).
followed and the treatment was kept up until the 40th day—when they were finally discontinued. The patient stated that he felt a new man after each injection that he was conscious of. The lungs cleared up without any trouble. The diagnosis in this case was confirmed bacteriologically.

Perhaps the most extensive use to which this serum has been put, is in the treatment of Puerpural Septicaemia and although in many cases most gratifying results have been obtained still the general consensus of opinion is, that its action must be
regarded as somewhat uncertain.

The committee of the American Gynecological (20) Society in 1899, found that in 534 cases in which it had been used there were 20.6 per cent deaths not an encouraging result. It must be noted however that the reports were based on the most severe cases.

Their conclusions were summed up as follows:

When the streptococci were positively demonstrated the mortality was 33 per cent. This fact would demonstrate that a serum which is obtained from a given Streptococci may protect an animal from that organism but may be absolutely inefficient against another Streptococcus.

(After some points in the local treatment of this condition have been discussed they go on to say)

"That the committee find nothing in the literature clinical or expermental or in their own experience to indicate that its employment may markedly improve the general results in the treatment of this condition. One member of the committee was of the opinion that it had no deleterious effect upon the patient and therefore it may be tried if desired."

The opinion on this side of the Atlantic as to
(27) Its value in Puerpural cases would seem to be much the same, since at the British Medical Association Meeting in the same year Dr. Herbert Spencer gave the following brief summary of the view of leading Gynaecologists:-

1. "That as usually applied it has no scientific basis.

2. That it has not lowered the mortality of Puerpural sepsis.

3. That it usually lowers temperature and sometimes improves the general condition.

4. That its use is not free from danger.

As regards the last proposition there is a difference of opinion, and any danger attending the use of the serum probably arises either from carelessness in its preparation or want of cleanliness in its administration.

The views at present held as to the etiology of this condition certainly seem to justify some of the criticisms passed on the therapeutical value of the serum, especially when the following varieties of pathogenic bacteria are now considered capable of producing Puerpural Fever.
1. *Streptococcus pyogenes puerperalis.*
2. *Staphylococcus pyogenes aureus.*
3. *Gonococcus Neisser.*
4. *Bactereum Coli Commune.*
5. Certain other anaerobic bacteria of unknown biological properties.

It must however be born in mind that the first named is by far the commonest. It is at present considered impossible to draw a distinction between Puerpural Fever due to bacterial toxins alone and one due to the penetration of the bacteria themselves into the tissues. Having regard therefore to the many and complex Etiological factors associated with this condition it is easy to see that such a serum as the one under consideration must of necessity possess, in this connection, a very limited sphere of action.

One of the earliest uses to which this serum was put was in the treatment of Erysipelas. Shortly after its introduction Prof: Mornarek said he had used it in 46 cases with good results. (29)
Parascandolo however two years later pointed out as a result of his researches into the relationship between the Streptococcus pyogenes and the Streptococcus Erysipelatosus that "The serum of an animal immunised in respect of one of these organisms prevented the growth of a culture of the same organism in vitro and also cures animals into which such a culture has been injected. Neither microbe has however these actions in respect of the other; thus the serum of an animal immunised against pyogenes has no curative effect upon another suffering from Erysipelas. He therefore concluded that the organisms are specifically different and advocated the preparation of a serum from cultures of Streptococcus Erysipelatosus for use in the treatment of Erysipelas."

These views do not seem to be altogether born out in practice for I have collected the particulars of the following cases as being good examples of the benefit arising from the use of the ordinary Antistreptococcic serum.
Case 1. By Dr. Friel (Waterford) (31)

Patient a gentleman aged 61 of good constitution and active habits. Had severe facial Erysipelas with copious formation of bullae. On the third day 10 C CM were injected and a similar amount six hours later; and repeated during the next two days. The patient's condition rapidly improved; the subsidence of the constitutional symptoms being particularly well marked.

Mr. Bokenham made a plate-culture from the serum obtained from one of the bullae and an absolutely pure culture of Streptococci was yielded.

Case 2 (32)

By Mr. Bertram Thornton (Margate).

Patient a middle aged labourer began with Erysipelas which developed into severe Septicoæmia and Pericarditis. The case appeared hopeless. Pure cultures of Streptococci were obtained from the blood. On the fourteenth day 10 C CM of the serum were injected twice and daily for eight days following. Improvement was marked after the first dose and the man made a
rapid recovery.

Case 3. (33.)

By Dr. Harrison (Mossley)

Mrs. H aged 26. commenced with facial Erysipelas which in four days covered the entire face and involved the submaxillary region. A few days later a bedsore formed over the sacrum and another on one buttock. Nine days later she was practically moribund and the pulse could hardly be felt. She had been delirious for some days. 20 C CM of serum were injected and four hours afterwards she regained consciousness. She became delirious again shortly after but this disappeared after another injection. The injections were continued twice daily and in three days time she was able to sit up in bed and made practically an uninterrupted recovery.

Case 4. By Dr. H. Leslie Jones (Manchester) (34)

Mrs. S., aged 63. Commenced with an Erysipelatous patch on the forehead and extended down the nose. This gradually got worse and in a week the features were quite indistinguishable.
and the patient was unconscious; temperature 105°. Pulse indefinable. 20 C CM were injected and the following morning consciousness began to return. 2 injections of 10 C CM each were given and she began to make a rapid recovery which was quite uninterrupted.

Case 5. By Dr. Macmillan (Prestwich) (35)

Mrs. H commenced with small Erysipelatous patch on the right side of the face. By the evening of the third day the whole of the face and part of the scalp were involved. Prostration was extreme; temperature 103.6° pulse 130.

10 C, CM. of serum were at once injected followed in the morning by another 10 C CM. and in the evening there was considerable improvement as regards the intensity of the Erysipelas. The injections were continued for a day and she made a rapid and uneventful recovery.
As from many cases of Erysipelas, pure cultures of Streptococci have been obtained, it is easy to understand that the results of treatment by the serum must of necessity be more encouraging than in the case of some other acute infections of more doubtful nature.

.........

Beside the particular varieties of Streptococci infection referred to above, the serum has been extensively used in Septicæmia following wounds. In many instances the results have been most gratifying and in others practically no improvement has accrued from its employment. In such examples as these, a vigorous local treatment is generally carried out and it is consequently very difficult to determine how much benefit is due to the serum and how much to other agencies.

The following case of Septicæmia following a prick illustrates the value of the serum in this
connection.

(36) Case of Acute Hemorrhagic Septicoemia treated by Antistreptococcic serum.

Reported by;
Mr C. A. Ballance and Mr F. C. Abbott.

Dr. G. M., aged 30, pricked his thumb in making a postmortem examination on a case of suppurative peritonitis. Six hours afterwards the thumb began to throb and become painful. Four hours later the red lines of lymph duct inflammation had extended to the axilla, the glands of which soon became enlarged. Early next morning the pain and tension in the pad of the thumb, had become so great that an incision was made for its relief. Previous to this, vomiting had occurred with several shivering fits. The next day the whole body was covered with a scarlet septic erythema. The condition gradually got worse and by the evening of the following day the temperature was 104.7° pulse 150. Drowsiness was a prominent feature, Cough troublesome, nourishment taken with difficulty. No swelling of thumb and no discharge from the incision.
There was great pain and tenderness along forearm and arm. Axillary glands large and tender. Tongue coated and dry. He was fast passing into a typhoid condition. At midnight 3:5 C.C.M. ANTISTREPTOCOCCIC serum was injected and repeated every four hours. Six hours after the first injection, certain improvements were manifested.

1. The mind was clear and the headache had disappeared.
2. The respirations were regular and less rapid.
3. The pulse was slower.
4. The tongue was moist along the edges.

The next day he was very weak, temperature being 104°F. continuously. He had epistaxis towards evening and owing to his prostrate condition Strychnine and digitalis were ordered every four hours. During the night the temperature dropped and much pain and some swelling were noticed in the ball of the thumb. The next day an incision was made into the thenar eminence and the sheath of the tendon opened but no pus was evacuated. At midday the dose of serum was doubled 7 C.C.M. being given every four hours. From this time he gradually became convalescent, and made a perfect recovery. No further incisions were necessary.
as the local condition speedily subsided. The wound healed without suppuration and the threatened inflammation under the anterior annular ligament subsided.

(37) Dr Jameson reports a case in which he successfully treated a chronic purulent discharge from broken-down axillary and supra-clancular glands. The serum was commenced sixty-two days after the abscess was opened. Five daily injections of 3-45 C. CM. each were given into the great pectoral muscle. He then made an uninterrupted recovery.

(38) Mr Crossing and Dr Webber report a fatal case of acute Septicemia in a girl aged 15½; which commenced as a small pustule the left side of the lower lip. The swelling quickly involved the greater part of the face and below the chin. The swellings were repeatedly incised. The lungs were to a certain extent involved. The serum injections were commenced on the seventh day and in all 20 C. CM. were injected. She died two days later. The reporters are of opinion that possibly
the serum was not used early enough, and not in sufficient quantity.

The notes of the above case do not show that any bacteriological examination was made. It is quite possible however that this was an example of a mixed infection and if this was the case the fatal result is more easily explained.

The following instance which occurred in the experience of Mr Paget exemplifies this point.

(39) The patient a man aged 32 noticed five days before admission to hospital, a small pimple on the skin of the upper lip which he poulticed. In the course of a day or two, the lip began to swell and the next day a little blood and pus came from the sore spot. The day before admission he had rigors, chills and sweating. On admission the upper lip was greatly swollen, hard and dusky and showed one or two points of suppuration. It was at once incised, but no definite abscess was found. On the next day his general condition was worse and he complained of pain in the right side and back.

Two injections of ANTISTREPTOCOCCIC SERUM
were given (10 C.CM. each time) and at midnight three more incisions were made but no pus found.
The next day three more injections (10 C.CM. each) were given and he seemed on the whole better. The next day he was in every way worse, delirium, restlessness, hard infiltrating swelling over the whole side of the face, and oedema of the neck. In the afternoon 10 C.CM. more serum were injected and in the evening the lips and cheeks freely incised, a little pus escaping from one of the incisions.
The next day he was much worse and two more injections were given; but he died shortly after midnight. A bacteriological examination of the blood of this patient during life indicated that the case was one of mixed infection, as the Streptococcus was not the only microbe present.

Watson Cheyne favours the use of Antistreptococcal serum as a prophylactic, as well as a curative agent in operations about the tongue or throat, as septic pneumonia engendered, in most if not all cases, by the Streptococcus pyogenes is very frequently the cause of death. He points out that irremediable damage is done to the body before the immunising...
material has time to do its work. He gives three
instances in which he used the serum before operating,
and in each case there was a remarkable absence of
the sloughing and septic trouble, especially apt
to occur, after such a procedure in these particular
localities.

Regarding the use of this serum in Malignant
Endocarditis.

Dr Cyril Ogle has compiled a list of 19 cases
in which it was employed. 13 cases died and 6
recovered.

Of the 13 fatal cases, in 4 streptococci alone
were found either before death in the blood, or
after, in the vegetations. 6 cases were due to
a mixed infection, chiefly with the Staphylococcus
and 3 were uncertain.

Of the cases that recovered; in two were
Streptococci demonstrated in the blood; in one, a
few Staphylococci were associated with short
Streptococci; and in the remaining three, no bacteria
were shown to be present.
He considers that in such cases an Anti-
staphylococcic serum should be employed along
with the Anti-streptococcic and refers to such a
case published by Moritz in which the patient
recovered.

........................................

The serum has been advocated in the treatment
of Scarlet Fever, but no definite opinion as to its
real value can as yet be advanced.

(42) Josias considered that after treating a number of
children suffering from this disease with serum
prepared from the horse and sheep, that pseudo-
membranous angina unaccompanied by suppurating
glands improved more quickly than usual. He found
that it had no effect on suppuration even though
due to Streptococci and none on albuminuria or
temperature. He gives the following table.

Mortality without serum 5.81% 
" with sheeps serum 2.08% 
" " horse " 5.31% 

Therefore lowest mortality obtained by treating with
least active serum.
In the report of the medical officer of the Local Government Board for 1899-1900, Dr. M. H. Gordon considers, that the essential agent in the production of this disease is a special Streptococcus Viz.: the "Streptococcus Scarlatina" which has a slightly different functional activity from the Streptococcus pyogenes. This fact would probably explain the want of success attending the use of the ordinary serum in these cases.

... . . . . . .

With reference to the use of this serum in Small pox, Lindsay finds that, in cases in which it is used, the critical period following the absorption of the pustules was shortened, the intensity of the toxemia seemed to be less and there was less tendency to Cardiac failure or collapse. Convalescence set in earlier and progressed rapidly. Four out of his six cases recovered and not one of the four developed a single abscess during convalescence. The bacteriology of this condition not having been thoroughly worked out, it is perhaps premature to express any decided opinion as to the ultimate success of an extended application of the serum in this...
connection. A form of Streptococcus is however to be demonstrated in variolous pus.

In the preceding pages, instead of entirely confirming my remarks to the instance which occurred in my own practice, I have endeavoured by a selection of cases from the experience of others, to indicate, so far as I am able, the position held by Antistreptococcic serum as a therapeutie agent.

It will be seen therefore.

1. That its successful application in a measure depends on a recognition of the microbe which is responsible for the infection i.e. it is useless to expect a favourable result in say Staphylococcic infection.

2. Even when Streptococci are demonstrated its employment is sometimes unsatisfactory; this is explained by the fact that a given sample of curative serum is only antagonistic to a like strain of Streptococci from which it has been derived. Therefore as has already been pointed out it is important to immunise the
animal against as many strains of this organism as possible.

3. Experience would point to the view that many forms of mixed infection might well be treated by a serum of polyvalent character derived from animals immunised against various forms of pathogenic bacteria.

4. That in certain forms of Septicœmia of more or less obscure character it seems to be of great value and this value will probably be further emphasised by the result of additional trials.

5. It should be used as early as possible in the course of the disease. For this reason it is imperative in doubtful cases to have a bacteriological examination of the blood and secretions. As the injections rarely cause any inconvenience, the application of the serum need not be delayed until the receipt of the bacteriological report: If the report contra indicates this particular serum, no harm has been done and if a positive report has been received much valuable time has been
6. As regards dosage 10 C. CM appears to be an average dose. In many instances the amount injected is too small. It is often well to commence with a large quantity say 20 C CM for one injection. This was the procedure followed out in the case which happened in my own experience.

7. Antistreptococcic serum is not antitoxic in the same other serums are. It is primarily Ante-bacterial but by its inhibitory action on these organisms, it at the same time lowers their toxin production.

As the bounds of our knowledge of many forms of bacterial infection become more extended, we may safely assume that this particular branch of Serumtherapy will obtain a wider recognition with more certain results.
BIBLIOGRAPHY.

The figures refer to corresponding numbers in the text.

2. Watson Cheyne in Allbut's System of Medicine Vol 1 page 590.
5. Osler, page 162.

(73).
40. Practitioner April '97 page 347.
41. Lancet, Vol 1 '03 page 722.

---o-0000o---