AN INVESTIGATION

INTO

THE PHENOMENA OF "SERUM DISEASE":

THE RELATION BETWEEN

ITS VARIOUS FORMS

AND

THE PROTEINS OF HORSE-SERUM:

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M.B., Ch.B., D.P.H.
1st. May 1918.
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INTRODUCTION

The observations which form the basis of this work were made in the City of Glasgow Fever hospital, Ruchill. Although, hitherto, considerable attention has been given to the various problems of anaphylaxis, our knowledge with regard to it and to the allied subject of "serum disease" is still far from complete. This latter condition is now well recognised and the fact that the proteins of horse-serum play a large part in its production is well established but, as yet, there has been no attempt to show the relation between the disease and the serum proteins in a more specific way. In this work a detailed investigation was carried out, the special objects of which were:

1. To show that there are distinct varieties of "serum disease".
2. To show that the proteins of normal or antitoxic horse-serum are distinct from each other in their characters and anaphylactic reactions.
3. To attempt to correlate specifically the various forms of "serum disease" with the various proteins of horse-serum.

At the same time an endeavour was made to obtain a clearer view of the various phenomena manifested in "serum disease" by clinical and statistical methods in the hope that the information that was obtained would prove of some material value. Incidentally some points of interest not directly bearing on the special object are also set forth.

The cases on which the observations were made were those of Diphtheria admitted into the hospital between March 1911 and June 1917, a great many of which were under the writer's care. The total number in which serum was administered was 4381.
The investigation is arranged in the following order:

INTRODUCTORY.

A. The Toxic Effects in Man of Injections of Antitoxic or Normal horse-Serum. ('Serum Disease?)
B. The Various Types of Serum Rash.

PART I. To Show that there are Distinct Varieties of "Serum Disease;"

A. Clinical Differences between the Various Types of Serum Rash.
B. Statistical Differences.
C. A Statistical Study of Other Symptoms of "Serum Disease;"
D. Appendix.

PART II. To Show that the Proteins of Normal or Antitoxic horse-Serum are Distinct from Each Other in Their Characters and Anaphylactic Reactions.

A. The Distinction in Characters between the Proteins of horse-Serum.
B. The Protein-Content of Antitoxic or Normal horse-Serum.
C. Anaphylaxis to the Separated Proteins of horse-Serum and Other Proteins.
D. The Presence of Precipitins in the Blood.

PART III. To Attempt to Correlate Specifically the Various Forms of "Serum Disease" with the Various Proteins of horse-Serum.

A. The Relation between Anaphylaxis and "Serum Disease;"  
B. The Specific Correlation of the Various Types of "Serum Disease" with the Various Proteins of horse-Serum.
C. Conclusions.
INTRODUCTORY.

A. THE TOXIC EFFECTS IN MAN OF INJECTIONS OF ANTITOXIC OR NORMAL HORSE-SERUM ("SERUM DISEASE").

B. THE VARIOUS TYPES OF SERUM RASH.
Ordinarily, with the exception of a little local irritation, the injection of antitoxin is not followed by any immediate local changes. If the hands, syringe, vessels, etc., are clean, abscesses very rarely develop, provided that the serum is sterile, and, even if it is not, infection frequently does not follow.

It was early noted, however, (Lublinski, 1894) that injections of antitoxin were sometimes followed after a few days by a peculiar train of symptoms which are now spoken of as the phenomena of "serum disease," a condition which is recognised as allied to "Anaphylaxis." The symptoms principally noted were rashes, pains in the joints and fever. Scholz, in the same year, noted four cases. Since then the disease has become well recognised and was of fairly common occurrence in Diphtheria wards until the introduction of an antitoxic serum of high potency, since when the appearance of "serum disease," so frequent in the early days of antitoxic treatment, has diminished almost to vanishing point. The concentration of the serum would appear to have brought this about, as resort to the use of unconcentrated serum in the course of this investigation was followed immediately by the more frequent appearance of "serum disease" than had been experienced with the use of concentrated serum. In this connection Heinemann (1915) states that the refinement and concentration of serum eliminates in large measure the non-antitoxic proteins of the serum.

As serum treatment was extended to other diseases such as tetanus, streptococcal infection, etc., it was found that "serum disease" was not due to the antitoxic or antimicrobial principle in the serum but to the serum itself. Heubner and Bokay as early as 1895 expressed the view that the phenomena were due to other constituents of the serum.
than the antitoxin, viz. to the proteid non-antitoxic portion of the serum, and this was subsequently confirmed experimentally by Johanessen (1895) who found that the same phenomena were produced with normal horse-serum. Hartung (1896) collected statistics on the frequency of serum rashes and found that they occurred in from 8-11% of the cases.

Although our knowledge of "serum disease" is almost entirely derived from the use of horse-serum, it is known that the serum of other animals will give rise more or less markedly to the same effects.

The manifestations of "Serum Disease" in man, according to Pirquet and Schick (1905), may be:

1. The development of an eruption (serum rash) which is usually the first and most obvious indication of the disease and spreads from the site of injection over the rest of the body or appears simultaneously in symmetrical places.

2. A rise of temperature showing that the rest of the body is taking part in the reaction.

3. Synchronously with a rise of temperature, an increase in the pulse rate, its quality, however, remaining good.

4. Joint pains which are regarded as one of the most prominent symptoms. They bear some resemblance to an attack of rheumatic fever.

5. Enlargement of lymphatic glands in various parts of the body.

6. Oedema of loose tissues, generally of a slight nature and demonstrated by its being visible or by increase in the body weight.

7. Rare mucous membrane symptoms and blood changes, e.g. diffuse bronchitis and leucopenia.
B. THE VARIOUS TYPES OF SERUM RASH.

The serum rash is recognised as one of the principal features of "Serum Disease" or antitoxic sequelae. They are of various kinds and were divided by Hartung (1896) into four main types:

1. Urticarial.
2. Morbilliform.
3. Polymorphous or Circinate.
4. Scarlatina-like rashes.
   A. Diffuse Erythematous.
   B. Scarlatiniform.

The claims of the first three to be ranked as distinct types seem to be well established by all observers. The establishment of the scarlatina-like rash as a distinct type does not, however, meet with general approval. With the majority of observers, its occurrence at all is rare. Leiner (1902) states that it is contagious and believes it to be true scarlatina, and others that it is frequently limited to the site of injection. Many, however, attribute a rash of this type to the antitoxin injection. The majority of those who support the latter view state that these rashes occur early, from the second day after injection.

The fact of this early appearance of a rash suggests the possibility of cross infection or concurrent infection, taking into consideration the fact that Diphtheria and Scarlet Fever are often coexistent and often mistaken for each other and consequently often found in the same ward. The group of cases recorded as having developed this type of rash is specially dealt with in the Appendix to Part I in connection with reported cases, but, as regards the special object of this work, this type is left out of consideration altogether, because, on investigation, considerable doubt was thrown on the supposition that rashes of this type were
caused by serum at all, the facts elicited pointing rather to their being cases of exanthemata and the conclusion arrived at, after a study of these reported cases, is that Scarlatiniform or Diffuse Erythematous rashes due to serum do not exist but are considered to be due to infection with the exanthemata notably Scarlet Fever. This view was taken chiefly because of the presence of exanthemata being discovered in the wards in which these alleged serum rashes occurred. It was considered that the association in a Diphtheria ward of a so-called Scarlatiniform or Diffuse Erythematous serum rash and co-existing exanthemata, such as Scarlet Fever and German Measles, within their respective incubation periods had a very important bearing on the question, so much so indeed as to discredit the assertion that such a type of serum rash exists.

There are therefore three types of rash - Urticarial, Morbilliform and Circinate which are universally accepted by all observers as being, without doubt, due to the injection of antitoxic or normal horse-serum and it is these three types with which this investigation deals.
PART I

TO SHOW THAT THERE ARE DISTINCT VARIETIES OF "SERUM DISEASE."

A. CLINICAL DIFFERENCES BETWEEN THE VARIOUS TYPES OF SERUM RASH.

B. STATISTICAL DIFFERENCES.

C. A STATISTICAL STUDY OF OTHER SYMPTOMS OF "SERUM DISEASE."

D. APPENDIX.
A. CLINICAL DIFFERENCES BETWEEN THE VARIOUS TYPES OF SERUM RASH.

The urticarial rash is an eruption which appears suddenly in the form of red blotches on the skin, irregular in shape and scattered more or less over the body surface, the region round about the site of injection being usually affected first. Not infrequently this local rash is the only symptom so far as the skin is concerned, later, in the majority of cases, wheals develop in the centre of the reddened areas. In a few cases the wheal formation is not distinctly seen but the resemblance to urticaria in appearance and distribution still remains. The eruption frequently disappears with equal rapidity leaving behind no trace of its existence, save perhaps a slight and transitory hyperaemia over the affected areas. The wheals vary in size and are most commonly small and about the size of a coffee bean. Occasionally, however, they are larger, cover a considerable portion of skin and have elevated flat surfaces. In colour, they are pink or white and are surrounded by an hyperaemic areola. They may be discrete and few or numerous and confluent and coalescent. They are firm and semi-solid to the touch. In contour they are roundish or oval-shaped but a variety of outlines may be found. Individual lesions change their appearance frequently and successive crops of wheals may continue to appear for two or three days. Occasionally, however, there may be only a few blotches which disappear within twelve hours. There may be some oedema in the vicinity of the wheals, especially where the skin is delicate and thin.

The subjective symptoms are due to the intense itching and irritation and vary according to the susceptibility of the patient, neurotic patients especially suffering great distress. All kinds of sensations are experienced - stinging, burning, pricking. Scratching to obtain relief is, therefore, common but this serves not only to further develop
the eruption but also to injure the skin.

The second type, the morbilliform rash, as its name implies resembles measles, so much so sometimes, as to cause trouble in diagnosis. The eruption consists of fairly well defined macules, smaller in size than those of measles, and varying in colour from red to reddish yellow, the deeper tints of red, seen in measles, being absent here. The eruption, also, is not raised so much above the skin as in measles and frequently begins round about the site of injection and not on the face but spreads to the face later. It does not last so long as the eruption of measles and occurs most frequently on the extensor surfaces of the extremities though the trunk may be involved also. The conjunctivae may be injected and the eyelids puffy and, if the eruption is present on the face trunk and limbs, the patient presents an appearance which resembles measles very strikingly. There is usually, however, no catarrh and Koplik's Spots are not present. Individual lesions may be discrete or confluent but the crescentic character of the eruption, as noticed in measles, does not occur.

Subjectively there may be some slight irritation of the skin surface but nothing in comparison with the distressing irritation of the urticarial eruption: the constitutional disturbance, however, as will be shown later, is much greater in this type than in the urticarial.

The polymorphous or multiform erythema at first amorphous in arrangement tends to become circinate and form gyrate patterns. The lesions consist of erythematous maculae and are distributed over the body frequently in patches, different appearances being seen in different places. It is most commonly found over the knees, elbows, inner sides of thighs and over the back, spreading subsequently to the face and arms. The lesions are more or less flat. The macule consists of a central depressed area, where the colour is pale, and a peripheral extension of the erythema.
in the form of a ring. The colour of the ring, which is dark red or purple, varies in shade in different parts of the body. There may be some extravasation of blood into the skin, producing, as the rash fades, a variety of colours. Subjectively the eruption causes a smarting sensation which is insignificant compared to that of the urticarial eruption.
Leaving out of account for the present the Scarlatiniform, or diffuse erythematous rash, it will be noticed that there are three types of serum rash, Urticarial, Morbilliform and Circinate and these are seen to be essentially different in their clinical appearances from each other. Although, sometimes, there may be a little difficulty and confusion one with the other where the rash is not well marked, in the great majority of cases the clinical features of each are quite distinct and separate. The latter two, viz., the morbilliform and circinate, are more apt to be difficult to distinguish from each other than from the urticarial. Confusion appears to have been caused by mixed appearances of the rash in certain cases. This may be due, as will be shown later, to the possibility of two separate rashes being present at the same time.
B. STATISTICAL DIFFERENCES.

The total number of cases dealt with are the cases admitted certified as Diphtheria, between March 1911 and June 1917 and, although some proved not to be Diphtheria, serum was administered in each case.

Total Number of Cases Admitted - 4381

Total Number of Cases which Developed "Serum Disease" - 415 - 9.5%

Total Number of Serum Rashes - 435

**TABLE I**

CASES RECORDED AS SERUM RASHES

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Type</th>
<th>Number of Cases</th>
<th>Number of Rashes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP A</td>
<td>Type not stated</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>GROUP B</td>
<td>Type Scarlatiniform or Diffuse Erythematous</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>GROUP C</td>
<td>Accelerated Reactions</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>GROUP D</td>
<td>Type Urticarial, Morbilliform, Circinate Occurring after one injection of Serum</td>
<td>266</td>
<td>281</td>
</tr>
</tbody>
</table>

Total, |

415    |

435
It will be seen from the figures given that 9-10% of the cases developed serum rashes. 121 cases (Group A) were recorded in the Ward Journals as serum rashes but no type was stated, in consequence of which these cases were found to be of no value to this work and had to be discarded. Other information relative to this group was collected and tabulated but had to be discarded also, as it was of no value without the type of rash.

Group B comprised those cases which have already been mentioned as belonging to the 4th. type of rash (Scarlatiniform or Diffuse Erythematous) and, as stated before, are definitely recorded in the Ward Journals as serum rashes of that type but for the reason given were discarded.

Cases, Group C which showed Accelerated Reactions i.e. "serum disease" occurring in cases, which had received serum on two or more separate occasions, are also discarded so as to eliminate possible error. A reinjection of serum being associated with a shortened period of incubation and giving rise to more rapid and more acute symptoms than in a normal person.

Group D contains the cases with which this work deals. The records of these cases have been examined with scrupulous care and the information given regarding them subjected to the closest scrutiny. The analysis has been made of the number of rashes and not of the number of cases. The number of rashes, which were observed as having occurred after one injection of serum, is seen to be 281. Percentages are given as well as numbers so that comparison is made easy.
A subdivision of Group D shows (Table II) the number of rashes present in each case. In 251 cases the rash was single, and in 15 cases two rashes were observed. In the General Analysis these double rashes were counted separately but, in the Appendix to Part I, are also dealt with by themselves, because it was found that a study of these cases with more than one rash had an important bearing on the special object of this investigation.

A further subdivision of Group D, according to the type of rash present in each case, shows (Table III) the relative frequency of occurrence of each type. According to the results obtained, the urticarial type was found to be by far the commonest and this is confirmed by
most observers. This type represented 77.6% of the total, the morbilliform being intermediate with 15% and the circinate least common with 7.4%. The ratio between the three types shows that the urticarial is ten and a half times and the morbilliform twice more frequent in occurrence than the circinate. The frequency of occurrence of the three types has been noted before in other works but great divergence of opinion seems to exist. Most observers are agreed with regard to the urticarial type being the commonest but the position of the other two does not appear to have been worked out satisfactorily. This may, possibly, be due to several causes. In the first place the number of cases dealt with by many observers does not seem to be great enough to form definite opinions or to draw warrantable conclusions.

Secondly, it may be due to the fact that morbilliform and circinate rashes are the two most likely to be confused with each other, and, thirdly, the constituents of serum may vary as Goodall (1907) states according to the source and may possibly account for varying results obtained. The regularity of the order of occurrence does not appear, however, to have been so fully investigated. Park and Bolduan (1908) state that the morbilliform rashes invariably follow the urticarial and the reverse order is rarely or never observed and that the circinate also usually follows the urticarial. Goodall states that urticaria usually precedes the circinate type.

By a careful study of the figures given in the analysis (Table IV), the order of occurrence of the three types would appear to be distinctly traced throughout and would also seem to be fully demonstrated in the study of cases having more than one rash. It will be noted, also, throughout the whole statistical analysis, that the order in which the three types are repeatedly placed is a very striking feature and is possibly of some significance.
CLASSIFICATION AND GENERAL ANALYSIS OF RASHES.

1. Incubation Periods.

In common with other exanthemata a period of time elapses from the injection of serum until "serum disease" manifests itself clinically. To this interval of time the term "incubation period" has been applied and this period reckoned in days will be found in the first column of Table IV. The capital letters U, M and C used throughout the analysis represent the Urticarial, Morbilliform and Circinate types respectively.

<table>
<thead>
<tr>
<th>No. of Days after Injection of Serum</th>
<th>T O T A L C A S E S</th>
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<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>9</td>
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<tr>
<td>5</td>
<td>9</td>
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<tr>
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<td>17</td>
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<tr>
<td>18</td>
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</tr>
<tr>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Totals,</td>
<td>218</td>
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</tbody>
</table>
By a study of the number of rashes of the urticarial type found in the second column of this table it is seen that the earliest appearance of an urticarial serum rash was observed to be the 4th. day after injection of serum. The rashes increase in number, as the incubation period lengthens, up to the 7th. day on which occurred the maximum number of rashes. The number of rashes then gradually decreases, as the incubation period lengthens, until the last one recorded is seen to have occurred on the 18th. day after injection of serum. There was no urticarial serum rash recorded as having occurred at an earlier period than the 4th. day or later period than the 18th. day. The average incubation period for the urticarial type (arrived at by taking into consideration the number of rashes occurring on each day) was found to be the 9th. day after injection of serum.

Taking, similarly, the next column (3) showing the number of morbilliform rashes it is seen that the earliest appearance of this type is the 4th. day after injection of serum. As the incubation period lengthens, the number tends to increase also but very irregularly up to the 14th. day when the maximum number is recorded, and then, continuing in decreased numbers up to the 16th. day, the rashes cease altogether.

A notable feature in this column is the blank recorded on the 5th. day and again on the 6th. day, no misses being found on the subsequent days. This feature tends to give an isolated appearance to the single case recorded on the 4th. day and this case was made the subject of special enquiry and great care was taken to verify this peculiar result. The case was found, however, to be quite authentic. The reason may be that the number of cases of this type is after all a comparatively small one. The minimum and the maximum incubation periods for this type are therefore the 4th. and 16th. days respectively, the average period being the 12th. day after the injection of serum.
Turning now to the next column (4) containing the number of circinate rashes, it is seen that the earliest appearance of this type is the 11th. day after the injection of serum, the maximum number occurring on the 15th. day and the last one being recorded on the 19th. day, the average incubation period being the 14th. day after injection of serum.

The minimum, maximum and average periods of incubation for the different types are given in condensed form in Table V.

<table>
<thead>
<tr>
<th>Incubation Periods in Days</th>
<th>U</th>
<th>M</th>
<th>O</th>
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<tr>
<td>Minimum</td>
<td>4</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Maximum</td>
<td>18</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Average</td>
<td>9</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

By studying now, as a whole, the columns showing the numbers of the three different types of rash, it may be observed here that the more cases dealt with the more uniform and reliable the results will be. The number of urticarial rashes would appear to be sufficient to obtain conclusive and definite findings and perhaps to ignore altogether possible error, and, although the number of morbilliform and circinate rashes is not very great, these rashes may be sufficiently numerous to warrant the conclusions drawn.

It has already been noted that, according to the results obtained in this work, the frequency of occurrence is in the order, urticaria first, morbilliform intermediate and circinate last. More important, however, than the relative frequency of occurrence is the order in which the different types occur. Looking at the table as a whole the order of occurrence of the different rashes would appear to be distinctly traced throughout.
The urticarial rashes appear, reach their maximum and cease at an earlier period than the morbilliform and still more than the circinate. The maximum number of urticarial rashes occurs on the 7th. day, a period when the morbilliform type is just beginning and the number of the urticarial rashes is rapidly decreasing before the circinate commences. Similarly though not so distinctly, perhaps, the morbilliform rashes have made their appearance considerably before the circinate type begins.

The greatest distinction is observed between the urticarial and the circinate types and this observation is so strikingly similar to an analogous occurrence in the causation of anaphylaxis by the different serum proteins as to be carefully noted and borne in mind.

This order of occurrence of the different rashes is in accordance with the views of Goodall, Park and Bolduan and others whose observations were, however, merely general statements and not apparently founded on statistical analysis such as has been done here.

The incubation periods of the different rashes are not so distinct from each other as to allow of the possibility of a rash being diagnosed by its time of appearance alone, e.g. there is a period according to Table IV from the 11th. to the 16th. day in which a rash belonging to any of the types might appear. Moreover during this period more than one type of rash might make their appearance in the same patient, even conceivably, at or about the same time. That this does happen is the firm belief of the writer and, moreover, may account for the presence of so-called mixed rashes, noted by some observers, e.g. Park & Bolduan, v Pirquet & Schick, Goodall and others. Even earlier than the 11th. day urticarial and morbilliform rashes might make their appearance together and therefore a diagnosis of the type of rash could not possibly be made from a study of its incubation period, the only conclusion that
might possibly be drawn would be that the earlier a serum rash appeared the more likely would it be of the urticarial type, and the later it appeared the more likely would it be of the circinate type.

It will be observed, also, that the average incubation periods (Table V) for the urticarial, morbilliform and circinate types are respectively 9, 12 and 14 days. Again the gradation is in the order urticarial, morbilliform and circinate, the distinction being most marked in the case of the urticarial and the circinate and less marked, but quite distinct, between the morbilliform and the circinate. The other columns in Table IV show the percentage incidence of the incubation periods of the three types. They can thus be compared with each other on an equal footing and, in order that this comparison might be more easily seen, a graph has been drawn of these percentages.
GRAPH OF PERCENTAGES FROM TABLE IV.
It will be seen from the graph, perhaps even more clearly than from the table, the distinct difference between the three types.

The urticarial curve is much more regular in its course and less swinging in character than those of the other two, the cause of this difference being apparently accounted for by the greater number of cases of this type dealt with. A curious point is illustrated in the curves of the morbilliform and circinate types. Roughly speaking, between each incubation period the curves of these two types tend to cross each other in alternate sequence i.e. the curve of the morbilliform type tends to descend when the curve of the circinate type tends to ascend and vice versa alternately, e.g. between 12th. and 13th. days the curve of the morbilliform type descends whereas the curve of the circinate type ascends and between the 13th. and 14th. days the converse takes place, the higher readings on each day being alternately morbilliform and circinate and similarly with the lower readings.

No attempt is made to explain this curious phenomenon beyond stating that, possibly, with more cases to deal with, the curves might have been less swinging in character and more level and regular in their course. It might be found then that the curious course of the two curves is mere coincidence and not capable of any scientific explanation.

A glance at the graph shows the marked difference and more or less isolated position of the urticarial curve from the other two, especially from the circinate. The highest point (18%) is distant in a horizontal direction a matter of 7 days from the highest point of the morbilliform (24%) and 8 days from the highest point of the circinate (33%). The distinction between the other two types is not nearly so marked but yet quite distinct. The curve of the circinate type tends to be later than that of the morbilliform, the highest points of each being distant in a horizontal direction from each other a matter of 1 day.
These highest points represent the days in which the greatest percentage of each type occurred and are not to be confused with the average incubation periods given in Table V which shows even more difference in the number of days between.

Comparing the bases of the three curves it is seen that the distance between the minimum and maximum incubation periods of the 3 types (noted in condensed form in Table IV) is 14, 12 and 8 days in the order urticarial, morbilliform and circinate respectively. It would be expected, therefore, that the highest points in a vertical direction of the curves of each type would show a converse difference and this is what is actually found. The highest point of the circinate curve is seen to be 33\%, of the morbilliform 24\%, and of the urticarial type 18\%, the difference between the first two being 9\% and the last two 6\%. The differences, as shown by the graph, between the three types therefore are:- in the distance between their minimum and maximum incubation periods; in the highest points of their percentage incidence; and in the incubation periods on which these highest points occur.

In the urticarial type the range of the incubation period is 14 days, the curve is longer and more spread out, the highest period is lower than in the other two and the greatest percentage of cases occurs on the 7th. day.

In the morbilliform type the range of the incubation period is 12 days, the curve is shorter than in the urticarial type and longer than in the circinate type, the highest point is higher than that of the urticarial type and lower than that of the circinate type and the greatest percentage of cases occurs on the 14th. day.

In the circinate type the range of the incubation period is 8 days, the curve is shorter than those of the other two and the greatest percentage of cases occurs on the 15th. day.
These differences between the curves of the three types show that the character and course of the curve of each is different and distinct from the others. They also show that there is a gradation in the order of occurrence of each type, the order being urticarial first, morbilliform intermediate and circinate last.
2. Duration of Serum Rashes.

TABLE VI

<table>
<thead>
<tr>
<th>No. of Days</th>
<th>TOTAL CASES</th>
<th></th>
<th></th>
<th></th>
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<td>5</td>
<td>51</td>
<td>21.4</td>
<td>23.7</td>
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<tr>
<td>2</td>
<td>58</td>
<td>18</td>
<td>10</td>
<td>26.6</td>
<td>43</td>
<td>47.6</td>
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</tr>
<tr>
<td>3</td>
<td>28</td>
<td>11</td>
<td>3</td>
<td>12.8</td>
<td>26.1</td>
<td>14.2</td>
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<tr>
<td>4</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>6.9</td>
<td>7.1</td>
<td>9.5</td>
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</tr>
<tr>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1</td>
<td></td>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>218</td>
<td>42</td>
<td>21</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

By a study of Table VI, the duration of the rash in each case is seen. Dealing with the column of percentages of each type of rash, it is observed that 51%, or slightly more than half the number, of rashes of the urticarial type are present only for one day and here it may be noted that fractional parts of a day are counted as one day and in the case of the urticarial rashes many did not last the full 24 hours. By comparing this figure with the corresponding figures of the morbilliform and circinate types it is seen that the percentage of these latter is less than half that of the urticarial being 21.4% and 23.7% respectively. The figures in the case of two day's duration of the rash show almost a converse result. That of the Urticarial type 26.6% is almost half those of the Morbilliform and Circinate types which are 43% and 47.6% respectively. As the days of duration increase, the percentage duration of urticarial rashes decreases uninterruptedly from the 1st. day until the 6th. day.
longer than which no urticarial rash was observed to have lasted.

In regard to the other two types the same uninterrupted but more abrupt and less gradual decrease in percentage duration takes place after the 2nd. day, the longest duration of the morbilliform being 6 days and of the circinate 8 days.

It is apparent that the duration of rashes of the urticarial type is shorter than that of the other two.

A discrimination between the morbilliform and circinate types is more difficult to be made. The difference between their respective figures for the first day is very little the excess being in the circinate column. The difference between their respective figures for the 2nd. day is a little more than on the 1st. day and the excess is again in the circinate column. The difference between their respective figures for the 3rd. day is more marked and the excess is this time in the morbilliform column and, although the morbilliform figure for the 4th. day does not show excess over the corresponding circinate figure, and although the longest duration of the morbilliform rash is 6 days, it would appear, nevertheless, that the duration of the morbilliform rash is slightly longer than that of the circinate rash.

If more cases of each type had been available, the distinction might possibly have been more marked but, nevertheless, the number of cases dealt with and the figures given seem to be sufficient to warrant the conclusion.

In regard, therefore, to the duration of each type of rash, it would appear that the urticarial type is of shortest duration, the circinate being intermediate, and the morbilliform type of longest duration, thereby showing in the attempt to prove that they are distinct another way in which the three types differ from each other.
The conclusions drawn from a study of the clinical and statistical differences between the three types of rash may now be stated in condensed form according to the results obtained in this work.

1. The three types of rash differ from each other:
   (a) in their clinical appearances and manifestations.
   (b) in their relative frequency of occurrence.
   (c) in their minimum and maximum incubation periods and in the length of the interval of time between these two points.
   (d) in their average incubation periods.
   (e) in their order of occurrence.
   (f) in the character and course of their graphs.
   (g) in their duration.

II. The relative frequency of occurrence of the three types is urticarial most frequent, morbilliform less frequent and circinate least frequent.

III. The order of occurrence of the three types is urticarial first, morbilliform second and circinate last.

These conclusions, which tend to show that the three types of rash are quite distinct from each other, suggest, therefore, the possibility of the cause of each type of rash being also different and distinct. The distinction, already observed between the three types by a study of the rashes, becomes even more marked in an investigation of some of the accompanying symptoms of "serum disease" and the theory that the causal factor in each type is not the same but of different origin is considerably strengthened.
Each type of serum rash may now be compared according to the other symptoms of "serum disease" present in each case. The most important accompanying symptoms are pyrexia, joint pains, oedema, enlarged glands and increase in the cardiac dullness.

I. STATE OF THE TEMPERATURE IN CASES OF "SERUM DISEASE"

### TABLE VII

<table>
<thead>
<tr>
<th>Temperature</th>
<th>TOTAL CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td></td>
<td>U</td>
</tr>
<tr>
<td>None</td>
<td>174</td>
</tr>
<tr>
<td>(A) elevated but accompanied by other symptoms</td>
<td>29</td>
</tr>
<tr>
<td>(B) elevated no other symptoms</td>
<td>15</td>
</tr>
<tr>
<td>Totals,</td>
<td>218</td>
</tr>
</tbody>
</table>

According to Ker, pyrexia is one of the most frequent symptoms and may, indeed, occur without other symptoms at all. It lasts usually as long as the clinical symptoms of "serum disease" and, in the more severe cases, is generally of the remittent type.

As will be observed from the table there are three groups under the heading of temperature. The first group comprises those cases in which pyrexia was absent altogether, the second in which pyrexia was present but was accompanied by other symptoms and the third those in which pyrexia was present unaccompanied by any other symptoms.

Other symptoms present were:
- Oedema, Joint Pains, Enlarged Glands.
The first group shows that in 79.3% of cases which had an urticarial serum rash there was no pyrexia at all, in 28.6% of cases which had a morbilliform serum rash there was no pyrexia at all, and in 14.2% of cases which had a circinate serum rash there was no pyrexia at all. That is to say the presence of pyrexia is least frequent, less frequent or more frequent according to whether the type of rash present is urticarial, morbilliform or circinate respectively.

In the second group (Group A) the elevation of the temperature is complicated by the presence of other symptoms and it is not possible to state to what single or combination of complications this pyrexia is due, therefore these cases are collected in a separate column. The information, however, that is given is of great value. The percentages show that pyrexia, when accompanied by other symptoms, is most frequently present when the cases are those in which a morbilliform rash occurs and that pyrexia, similarly complicated, is less frequent in cases in which a circinate rash is present and least of all in those in which there is a rash of the urticarial type.

Reading this in conjunction with the results noted in the third group this may mean that the other symptoms of "serum disease" in cases in which the rash is of the morbilliform type are inclined to be more severe in nature and accompanied by more constitutional disturbance than in cases where the rash is of the circinate or urticarial types and that the severity of the symptoms is in that order i.e. morbilliform most severe, circinate less so, urticarial least so.

The conclusion is confirmed by the results obtained on investigation of these other symptoms.

The third group consists of those cases of serum rashes in which the temperature was elevated and in which no other symptoms were present. The figures (6.9% of urticarial type 21.4% of morbilliform type and 42.9% of circinate type)
show that elevation of temperature, unaccompanied by other symptoms and, therefore, only to be accounted for by general reaction, least commonly occurs in cases in which the rash is of the urticarial type, that it more commonly occurs in cases in which the rash is of the morbilliform type and that it most commonly occurs in cases in which the rash is of the circinate type i.e. constitutional disturbance in "serum disease" unless other complications be present, is least, greater or greatest according as the rash present is urticarial, morbilliform or circinate respectively.

The minimum, maximum and average heights of the temperature are given in Table VIII.

<table>
<thead>
<tr>
<th>Height of Temperature</th>
<th>U</th>
<th>M</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>99</td>
<td>99</td>
<td>98.8</td>
</tr>
<tr>
<td>Maximum</td>
<td>103.4</td>
<td>104</td>
<td>103.5</td>
</tr>
<tr>
<td>Average</td>
<td>100.8</td>
<td>102</td>
<td>101.4</td>
</tr>
</tbody>
</table>

This Table includes all cases in which an elevation of temperature occurred and it will be observed that the average temperature is lowest, higher or highest according as the rash present was urticarial, circinate or morbilliform respectively and, as noted before, this order is probably due to the fact that general reaction, in the presence of other complications, is greater in cases showing morbilliform rashes than in the other two and in cases showing circinate rashes than in cases where the rash was urticarial. This confirms the view held by Pirquet and Schick. Axenow (1914) states that, in a series of 683 cases of "serum disease" the fever was slightest with urticaria.
2. DURATION OF TEMPERATURE WHEN NO OTHER SYMPTOMS ARE PRESENT (TABLE VII (B)).

Table IX gives in detail the duration of the temperature in those cases of rash and pyrexia that are unaccompanied by any other symptoms. (Group B of Table VI)

TABLE IX

<table>
<thead>
<tr>
<th>No. of Days</th>
<th>U</th>
<th>M</th>
<th>C</th>
<th>Totals</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U</td>
<td>M</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>53.4</td>
<td>55.6</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>33.3</td>
<td>22.2</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>13.3</td>
<td>11.1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td>Totals,</td>
<td>15</td>
<td>9</td>
<td>9</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

As will be seen from the table, in 53.4% of cases having an urticarial rash the duration of temperature is one day and in 55.6% of cases having a morbilliform rash one day (the figures for these two being nearly equal) and in 33.4% of cases having a circinate rash one day, (the figure in this case being lower). Similarly for two days duration of temperature the figures are 33.3%, 22.2% and 11.1% for cases having urticarial, morbilliform and circinate rashes respectively. 22.2% of cases having circinate rashes are the only ones where the duration of temperature was three days. For four days duration of temperature the figures are 13.3%, 11.1% and 22.2% for urticarial, morbilliform and circinate rashes respectively. In five days duration of temperature there are no urticarial cases 11.1% morbilliform and 11.1% circinate. These figures clearly show that the duration of temperature, in cases that do
not develop any other symptoms, is shortest in cases having urticarial rashes, longer in cases having morbilliform rashes and longest in cases having circinate rashes, thus bearing out the results found in Table VI viz., that the constitutional disturbance with serum rashes, in the absence of other symptoms of "serum disease," is least and lasts for a shorter time in cases having urticarial rashes, is greater and lasts for a longer time in cases having morbilliform rashes and is greatest and lasts for the longest time in cases having circinate rashes.
Temperature is a symptom which can be ascertained with absolute accuracy as it is recorded daily. With some of the other symptoms, however, such accuracy is not so easily obtained. The noting of symptoms in a Ward Journal depends on a great many conditions, viz., the conscientiousness, ability and carefulness of the Medical Officer and nurse in charge of the case, on the fact whether the symptom is subjective or objective, on the age of the person affected and his or her ability to complain of it. The symptoms, which are now going to be dealt with, all depend on these varying factors and therefore inaccuracies are much more liable to occur than in the recording of a throat condition, presence of rashes, etc., things which are the daily routine of the ward.

The sins, however, are those of omission and not so much of commission; that is to say, what information is given can be taken as reliable and trustworthy but it is possible that symptoms occurred in certain cases and were not recorded for the reasons given in the Ward Journals. If negative facts had been recorded as well as positive facts the statistics might have been thereby affected, for example - a case develops a serum rash but beyond its type and duration and the temperature present being recorded no more information may be given. In this case other symptoms may have been present but were not recorded. If these other symptoms were stated not to have been present, then our information with regard to this case would have been complete.

Now in the following cases that are dealt with, when no mention was made in the Ward Journals of the presence of certain symptoms, it was taken for granted that these were not present in those cases.

This method shows, as will be seen below, that the results
obtained in the statistics with regard to certain symptoms are fairly accurate, whilst with others they are probably inaccurate and this inaccuracy may be due to the fact that the symptoms in question have either not been observed or else not recorded in the Journal.

TABLE X

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>% of Total Cases (4381)</th>
<th>% of Total Rashes (281)</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>U</td>
<td>M</td>
</tr>
<tr>
<td>Joint Pains</td>
<td>1%</td>
<td>18%</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Oedema</td>
<td>7%</td>
<td>7-8%</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Albuminuria</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Enlarged Glands</td>
<td>4%</td>
<td>5%</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

JOINT PAINS

The joints involved in this series of cases were the ankle, knee, shoulder, elbow, wrist and finger joints. There was usually some swelling, little redness, but much pain and tenderness to touch. The complication resembles an attack of acute rheumatism but is not so severe and does not usually last so long. It does not respond, also, so well to anti-rheumatic treatment.

The frequency of joint pains has been noted by Hartung (6.7%) v Pirquet & Schick (1%) Barbier (1904) and Park & Bolduan less than 1%. The percentage of joint pains in the total cases in this work (4381) was found to be slightly more than 1%.

The percentage of joint pains accompanying at the same time or shortly after the rash was found to be 18%. The occurrence of joint pains alone i.e. without a rash was found to be very infrequent a point that is also noted by Ker.
The presence of joint pains is much more likely to be noted than some of the others, because it is a symptom that a patient would readily complain of.

As will be seen from Table X 12% of cases having urticarial rashes, 40.5% of cases having morbilliform rashes and 38.2% of cases having circinate rashes developed joint pains.

It would appear therefore that joint pains are more frequently present with morbilliform rashes, less so with circinate and least of all with urticarial, a result which is analogous to the order of the percentage figures given in Group A of Table VII.

It is quite possible, of course, that the presence of joint pains may be overlooked in the case of very young children who are not liable to complain of these pains but, comparing the figures obtained in this table and those in Group A Table VII, it would seem that the results closely correspond and therefore may be taken as fairly accurate. At any rate as far as the subject of this work is concerned a distinction would again seem to be drawn between the three types.

4. OEDEMA.

The oedema met with in cases of "serum disease" is usually of a slight nature affecting most frequently the face (causing a general puffiness) hands and arms and, more rarely, the dependent parts of the body, showing that it is not due to passive congestion.

Park and Bolduan state that oedema is a very frequent symptom.

The results obtained in this work are a little disappointing as it would appear from the figures given that oedema is an uncommon symptom.

According to the figures given in Table X, oedema is present in less than $\frac{1}{3}$ of the total cases and only in 7-8% of the
rashes.
The figures for the three types of rashes are too small for any definite conclusion to be drawn from them.

Oedema, when present, is usually of a slight nature and fairly transient in its duration. It also is not a subjective symptom as it rarely gives rise to discomfort, pain, etc., as would cause the patient to complain of it, consequently it is apt to be overlooked altogether and, even if observed, is not noted because of its short duration and also that, after the urine has been examined for albumen and found negative, the mind of the observer is set at rest and the oedema is treated as if it were of no consequence.

Another reason also is that the oedema may be only demonstrable by increase in the body weight according to the method of v Pirquet and, as this is not usually carried out as a routine procedure, any oedema that may be present is not observed.

It was noticed in a few cases that, when a serum rash with oedema was present, the urinary excretion was diminished in the early stages of the symptoms and gradually increased in quantity as these symptoms passed off. It is, therefore, possible that, as the diminution in the amount of urine occurs synchronously with the water-logging of the tissues, these two events are related to each other.

In this connection, a series of cases were weighed regularly once and sometimes twice a day during the attack of "serum disease". The time of weighing was approximately the same each day, the period before the mid-day dinner being chosen as the most suitable. The weights were recorded and alongside each day's weight was put the total urinary excretion for the 24 hours. The results showed that, when an increase of weight took place, the increase was observed usually on the day following the first appearance of the serum rash, though sometimes it was observed even on the same day. The increase was observed even when no obvious oedema was present and, by the time the serum rash had disappeared,
the weight of the patient had regained the normal. No appreciable difference could be made out, in the small number of cases dealt with, between the increase of weight for the three different types of rash.

It was also noted that, when the increase of weight was greatest, the urinary excretion was least. As the normal weight of each case had been previously ascertained, any increase that was observed must have been due to the "serum disease" and, according to the theory, this increase was due to a retention within the body of water normally excreted in the urine but in "serum disease" presumably causing a waterlogging of the tissues.

Oedema is a term usually used in medicine to refer to the areolar tissues being overloaded with fluid in a manner that pits on pressure. While this oedema on the surface of the body may occur in "serum disease" it is comparatively rare and usually trifling in character and certainly does not explain the great increase in body weight noted in many cases. What probably happens is that the whole lymphatic system of the body is congested. This applies to every organ and is exceptionally well seen in the muscles. It is only necessary to take the muscle between the finger and thumb and compare the resistance of a healthy muscle in a neighbouring child to appreciate that the oedema of "serum disease" has no relation to the oedema of cardiac disease.

Following up the question of oedema, cases which showed the presence of albuminuria have also been noted. It has been asserted that albuminuria was caused by serum injection. The figures given, however, would tend to discredit that assertion and to confirm the modern view, namely, that albuminuria has no relation to "serum disease," confirming thereby the statement of Ker.

As is shown on the table only 1 or 0.4% of cases having urticarial rashes showed the presence of albuminuria. With the other types there is no record of any case having
developed this symptom. Investigation of this case revealed the fact that the albuminuria had been present since admission and therefore was unlikely to be the effect of the "serum disease" which followed.

5. ENLARGEMENT OF GLANDS.

The presence of enlarged glands as a symptom of "serum disease" has been noted as being more often seen in severe cases of the disease.

The glands involved depend on the site of injection of the serum though, in some cases, extension to other groups of glands may take place.

The glands involved become quite palpable and stand out distinctly, pain and tenderness on pressure being marked features. Tenderness, as a rule does not last long.

In Table X the percentage of total cases having serum rashes which develop enlarged glands is seen to be 5%.

The percentage figures for the three types of rash show a preponderance in favour of the morbilliform type.

It has already been noted that pyrexia, when accompanied by other symptoms, is more frequently present, and the height of the temperature higher, in cases having morbilliform rashes. It has also been noted already that joint pains are common with this type, therefore it is no matter for surprise to find that such a sign of constitutional disturbance as the presence of enlarged glands is also more frequently met with in this type than in the other two.

These facts will confirm the statement already made that general reaction is greater with this type of rash than with the other two and greater with the circinate type than with the urticarial.
6. INCREASE IN THE CARDIAC DULLNESS.

Increase in the cardiac dullness in cases of "serum disease" has been noted in this investigation. Careful search of the literature elicits no information on this subject and therefore the following statistics are of considerable interest in the study of the disease.

Unfortunately cardiac measurements were not made in all the cases and, in some, detailed figures were not given, the information merely stating that the cardiac dullness was or was not increased. Out of 50 cases examined detailed information was given and accurate measurement made in 40 and in 10 cases the cardiac area was said to be either increased or not increased but no measurements were given. It would seem, however, that there is a sufficient number of cases examined to furnish useful information and from which to draw warrantable conclusions. The findings moreover have a distinct bearing on the special object of this work.

<table>
<thead>
<tr>
<th>Increase in the Cardiac Dullness</th>
<th>Total Number</th>
<th>%</th>
<th>Number</th>
<th>%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>U</td>
<td></td>
<td>M</td>
</tr>
<tr>
<td>Present</td>
<td>36</td>
<td>72</td>
<td>29</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Not Present</td>
<td>14</td>
<td>28</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Totals,</td>
<td>50</td>
<td>100</td>
<td>36</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

It will be seen from the figures given that out of the 50 cases examined 36 showed increase in the cardiac dullness and in 14 cases no increase was present, giving a percentage of total cases of 72 and 28 respectively. These cases are divided, according to the type of rash present in each case.
and the results, in the form of percentages, are seen in the right hand column of the table. From these it is seen that the percentage of cases which developed increase in the cardiac dullness is greater for those with urticarial rashes and a little less for cases with circinate rashes, and that these two exceed considerably the figure for the morbilliform rashes. In the second row of figures, in which is shown the percentage of cases which did not develop this condition, it is seen that the figure for the morbilliform rashes exceeds considerably those of the urticarial and circinate. The figure in the second row of the circinate column is slightly in excess of the corresponding figure in the urticarial column.

The total number of cases dealt with, especially as regards morbilliform and circinate rashes, is not large enough to draw definite conclusions as regards the relative frequency of occurrence of this condition in the three types of rash. The figures, however, as regards the 50 cases examined, show that increase in the cardiac dullness would appear to be more common with urticarial rashes, less common with circinate rashes and least common with morbilliform rashes. A much greater number of cases would require to have been dealt with in order to confirm this statement or otherwise.

AMOUNT OF INCREASE IN THE MEASUREMENTS IN CASES OF INCREASE IN THE CARDIAC DULLNESS.

As it was thought it would be of interest, the amounts of increase in the cardiac measurements are given in detailed form in the subjoined table.
## TABLE XII

<table>
<thead>
<tr>
<th>AMOUNT OF INCREASE</th>
<th>TRANSVERSE DIAMETER</th>
<th>U</th>
<th>M</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LEFT BORDER</td>
<td>RIGHT BORDER</td>
<td>UPPER BORDER</td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>2</td>
<td>12</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>1/8&quot;</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1/4&quot;</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3/8&quot;</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1/2&quot;</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5/8&quot;</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/4&quot;</td>
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<td>1</td>
</tr>
<tr>
<td>1,1/8&quot;</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd, Space to 3rd, Rib</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th, Space to 3rd, Rib</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd, Space to 4th, Rib</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Measurements Given</td>
<td></td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Totals,</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>4</td>
</tr>
</tbody>
</table>
The first column shows the degree of increase or whether there was no change in the various measurements. The other columns give the number of cases of each type opposite the respective degree of increase and under the various cardiac measurements viz., the transverse diameter of the heart, the left border, the right border, and the upper border. The increase of the transverse diameter is of course the sum of the increases in the right and left borders of the heart towards and away from respectively the middle line of the sternum.

The figures for the urticarial type show that, in regard to the transverse diameter of the heart, the maximum increase was found to be as much as 1 and 1/8th inch in one case but the most frequent increase was ½ inch.

As regards the left border of the heart only two cases showed no change. The maximum increase was seen to be 5/8th inch and the most frequent ½ inch and ¼ inch.

As regards the right border 12 cases showed no change, the maximum increase was ½ inch and the most frequent 1/8th inch.

As regards the upper border 15 cases showed no change, in 3 cases there was an increase from the 3rd. space to the level of the 3rd. rib, in 1 case there was an increase from the level of the 4th. rib to the 3rd. space and in 2 cases there was a decrease from the 3rd. space to the level of the 4th. rib.

In 8 cases belonging to the urticarial column no detailed measurements were given, it being simply stated that the heart was or was not enlarged.

These figures show that increase in the cardiac dullness affects mainly the left border of the heart and in a much lesser degree the right border and that the upper border is only in a few cases affected at all and may be decreased instead of increased.

The figures in the morbilliform and circinate columns are
not so numerous and gaps are common but, nevertheless, even in regard to these columns, the "no change" is seen to be in the right and upper borders of the heart and the increase is mainly in the left border.

The fact that these cases were examined and measurements made, on admission and again with the appearance of the rash, precludes the possibility of the measurement noted on the latter occasion being a normal one for the particular individual.

This increase in the cardiac dullness is a condition which makes its appearance about the same time as the serum rash and it is more or less sudden in onset. It is accompanied, moreover, by no discomfort, pain, dyspnoea, cardiac murmur or any other apparent symptom and it disappears just as quickly with the passing of the "serum disease". The heart sounds appeared normal.

The appearance of the condition about the same time as the commencement of the "serum disease" suggests the possibility of the two conditions being related.

Such a condition is capable of several explanations. First, the enlargement of the cardiac dullness may be due to the increase in the capacity of the cavities of the heart, that is, dilatation of the heart. According to Monro (1911), dilatation of the heart is due to various organic diseases of the heart and blood-vessels, to degenerate changes in the muscular fibre of the ventricles, to diseases of the lungs, acute diseases, and in consequence of prolonged high tension. Moreover, dilatation is a condition which does not appear quickly but supervenes in consequence of the above mentioned causes. Dilatation is also found to be more common in the right ventricle than in the left because its wall is thinner. Even at an early stage it is accompanied by other symptoms such as general impairment of bodily and mental vigour, fainting attacks, insomnia, palpitation and breathlessness and later on dropsy, dyspnoea and enlargement of the liver. Cardiac murmurs, also, are
often present due either to the original valvular lesion or to secondary incompetence.

From the fact that none of these symptoms are present in this condition of increase in the cardiac dullness and that the patient appears to be otherwise well and free from any organic disease (except, of course, Diphtheria) it would appear very improbable if not impossible that dilatation of the cavities of the heart is the cause of the condition.'

Hypertrophy of the muscular walls of the heart, either in conjunction with dilatation or by itself, is another possible cause of the condition. Hypertrophy is usually seen in the ventricle when the muscular walls become increased in thickness in order to overtake constantly recurring increase of work. The causes, therefore, of hypertrophy are practically the same as those mentioned in connection with dilatation, viz., various organic diseases of the heart, vessels and lungs. The symptoms found with hypertrophy are those really of insufficient hypertrophy or of the original cause of the hypertrophy along with, perhaps, some discomfort in the region of the apex of the heart and irregularity or undue frequency of heart action. Hypertrophy like dilatation does not make its appearance suddenly but is due to long continued presence of some cause. In the condition under discussion there is no known cause, there are no accompanying symptoms, and the condition appears and disappears fairly quickly. Therefore it is difficult to see how hypertrophy either by itself or along with dilatation could be the cause of the condition.

The theory put forward here, in attempting to give an explanation of this increase in the cardiac dullness, is that the condition is directly due to the effects of "serum disease!" It has been already noted that oedema occurs as an accompanying symptom of this disease but it is only on the surface of the body that oedema is actually visible.
It is possible, however, that increase in body weight may be contributed to by oedema of other tissues and organs and therefore the increase in the cardiac dullness may possibly be due to an oedema of the muscular wall of the heart. As noted in the Table XII, the increase is mainly in the left border of the heart and, as the wall of the left ventricle is thicker than that of the right, it is conceivable that there will be more oedema in the former than in the latter. The fact, also, that there are no signs and symptoms and that the condition appears and disappears quickly would seem to add weight to the evidence in favour of this theory.
In order to summarise the symptoms of "serum disease" that have already been dealt with in detail, Table XIII has been prepared.

**TABLE SHOWING THE VARIOUS COMBINATIONS OF SYMPTOMS**

<table>
<thead>
<tr>
<th></th>
<th>U</th>
<th>M</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Joint Pains</td>
<td>21</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>2. Oedema</td>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3. Enlarged Glands</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. Joint Pains &amp; Oedema</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5. Joint Pains &amp; Enlarged Glands</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6. Oedema &amp; Enlarged Glands</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total Number</strong></td>
<td>44</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td>20.2</td>
<td>50</td>
<td>42.8</td>
</tr>
</tbody>
</table>

The table shows the number of cases in which the various symptoms occurred either separately or in combination. The cases are divided into three columns according to the type of rash present with each. The total number of cases, with rashes of the urticarial type, which developed the various symptoms is seen to be 44: the total number of cases with rashes of the morbilliform type, which developed the various symptoms - 21: and the total number of cases, with rashes of the circinate type, which developed the varicous symptoms - 9. The percentage incidence of the various symptoms is seen to be 20.2%, 42.8% and 50%, according as the type of rash present in each case is urticarial, circinate or morbilliform respectively. The result would appear to show that cases having morbilliform rashes are accompanied by other symptoms more frequently.
than cases having circinate rashes and much more frequently than cases having urticarial rashes. If Table VII Group A is referred to, the figures given there show that pyrexia, when accompanied by other symptoms, is most frequently present when the cases are those in which a morbilliform rash occurs, less frequently present in cases in which a circinate rash occurs and least of all in cases in which an urticarial rash occurs. It is also seen that (according to Table VII Group B), when no other symptoms are present, the severity of an attack of "serum disease" is urticarial least, morbilliform greater and circinate greatest.

Reading those two tables (Tables VII and XIII) in conjunction the conclusions drawn are that, whereas the constitutional disturbance in the absence of other symptoms is greatest in cases having circinate rashes, less severe in cases having morbilliform rashes and least severe in cases having urticarial rashes, nevertheless when other symptoms are present, the constitutional disturbance is greatest with the morbilliform type of rash, less severe with the circinate type and least of all with the urticarial type.

It will be noted with regard to the column of Table VII (A) showing the number of cases that, whereas only 29 cases out of 44 (Table XIII) of urticarial type, which were accompanied by other symptoms, showed an elevation of temperature, all the cases (21 and 9 respectively) of morbilliform and circinate type which were accompanied by other symptoms showed an elevation of temperature. It will be noted also, in Table VIII, that the average temperature is highest for the morbilliform type of rash, less high for the circinate type and lowest for the urticarial type.

These facts all tend to show that the rash for an urticarial type is the mildest of the three as regards constitutional disturbance and that, though symptoms such as joint pains, etc. may be present, these do not in every case cause an
elevated temperature. On the other hand the rash of a morbilliform type is the most severe of the three as regards constitutional disturbance if accompanied by other symptoms and, if not, then it is not so severe as the rash of a circinate type. The difference, however, in severity between the three types is very much greater between the urticarial and the other two than between the morbilliform and circinate types.
PART I

D. APPENDIX

A. A STUDY OF CASES WHICH DEVELOPED MORE THAN ONE SERUM RASH.

B. A STUDY OF CASES RECORDED AS HAVING DEVELOPED SCARLATINIFORM OR DIFFUSE ERYTHEMATOUS SERUM RASHES.
### A. A STUDY OF CASES WHICH DEVELOPED MORE THAN ONE RASH.

**TABLE XIV**

<table>
<thead>
<tr>
<th>Consecutive Number</th>
<th>Incubation Period of Rash after Serum in Days</th>
<th>Type</th>
<th>Duration in Days</th>
<th>Maximum Height</th>
<th>Temperature</th>
<th>Day of Occurrence after Serum</th>
<th>Other Symptoms Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 M 14</td>
<td>U M 1</td>
<td>3</td>
<td>N11</td>
<td>102.6</td>
<td>15th-17th days</td>
<td>Oedema &amp; Joint Pains</td>
</tr>
<tr>
<td>2</td>
<td>10 M 16</td>
<td>U M 1</td>
<td>2</td>
<td>N11</td>
<td>102</td>
<td>15th-17th days</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 M 12</td>
<td>U M 1</td>
<td>1</td>
<td>N11</td>
<td>102.6</td>
<td>11th-15th days</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9 C 15</td>
<td>U C 3</td>
<td>2</td>
<td>N11</td>
<td>100.6</td>
<td>15th-16th days</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7 C 13</td>
<td>U C 2</td>
<td>1</td>
<td>N11</td>
<td>102</td>
<td>11th-15th days</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9 C 15</td>
<td>U C 2</td>
<td>2</td>
<td>N11</td>
<td>103.4</td>
<td>13th-16th days</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9 C 16</td>
<td>U C 1</td>
<td>1</td>
<td>N11</td>
<td>100.8</td>
<td>13th-17th days</td>
<td>Joint Pains</td>
</tr>
<tr>
<td>8</td>
<td>7 C 13</td>
<td>U C 2</td>
<td>1</td>
<td>N11</td>
<td>100</td>
<td>13th-14th days</td>
<td>Joint Pains</td>
</tr>
<tr>
<td>9</td>
<td>8 M 16</td>
<td>U M 1</td>
<td>2</td>
<td>N11</td>
<td>101.6</td>
<td>15th-17th days</td>
<td>Joint Pains</td>
</tr>
<tr>
<td>10</td>
<td>13 M 16</td>
<td>U M 1</td>
<td>1</td>
<td>N11</td>
<td>101.4</td>
<td>16th day</td>
<td>Joint Pains</td>
</tr>
<tr>
<td>11</td>
<td>7 C 15</td>
<td>U C 2</td>
<td>2</td>
<td>N11</td>
<td>101</td>
<td>15th day</td>
<td>Oedema &amp; Joint Pains</td>
</tr>
<tr>
<td>12</td>
<td>8 M 12</td>
<td>U M 2</td>
<td>1</td>
<td>N11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4 M 13</td>
<td>U M 1</td>
<td>3</td>
<td>N11</td>
<td>99.2</td>
<td>15th day</td>
<td>Joint Pains</td>
</tr>
<tr>
<td>14</td>
<td>11 C 14</td>
<td>U C 3</td>
<td>2</td>
<td>N11</td>
<td>99.4</td>
<td>15th day</td>
<td>Joint Pains</td>
</tr>
<tr>
<td>15</td>
<td>6 M 10</td>
<td>U M 1</td>
<td>2</td>
<td>N11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Cases which developed two rashes.
As stated before there were 15 cases which developed two serum rashes after one administration of serum. That one single injection of serum may produce two or even three distinct rashes separated by a definite interval, in which there is no rash nor other serum phenomena, is noted by Goodall. He gives 4 examples of cases in each of which a single injection was followed by two rashes with an interval of time between each rash.

It was thought that a study of these cases might furnish valuable information especially with regard to the order of occurrence of the three types of rash.

As can be seen from the table the incubation periods, the type and the duration of the rashes are given in separate columns and also the maximum height and days of occurrence of any accompanying temperature and any other symptoms present.

Taking the column of incubation periods it will be seen that the interval of time between each two is sufficiently long as to exclude the possibility of the two rashes observed being one and the same. If this column is read in conjunction with the column of duration of the rash it will be noticed that each primary rash has disappeared before the outcome of the second one.

Dealing now with the type of rash a remarkable feature is the fact that the urticarial type invariably comes first and that the morbilliform and circinate follow it. As regards the duration of the rash, the urticarial type is seen to be of shorter duration than the other two. It will also be noted, in the next column, that, as it so happens, each of the urticarial rashes was not accompanied by any pyrexia at all and that as a rule the rash, which follows the urticarial in each case, is accompanied by pyrexia, which lasts for a period varying from 1-5 days.
In the last column it is seen that other symptoms are present only with the second rash. The order of occurrence as regards the morbilliform and circinate rashes can not be made out from this table but, at any rate, it is clear that the urticarial comes first.

2. Case which developed three rashes.

This case "P P" developed an urticarial serum rash, the incubation period of which was the 8th. day after injection of serum. It lasted 1 day and there was no temperature. 72 days after the first injection the patient received another dose of serum and this was followed 5 days later by a morbilliform serum rash. This lasted 1 day and there was no temperature. 3 days later still, a third rash made its appearance and it was circinate in type. It lasted 2 days and was accompanied by oedema, joint pains and pyrexia.

This case is an example of the "Accelerated Reaction" and tends to illustrate and confirm statements made by certain observers on this subject. According to Abthus, a re-injection of serum is associated with a shortened period of incubation and gives rise to more rapid and more acute symptoms than after a single injection. According to Goodall, when a patient has had a serum reaction at the primary injection he is more likely to have an abnormal reaction after the 2nd. injection. Accelerated reaction is described by v Pirquet & Schick as a train of symptoms which differ from the results of a single injection in their earlier onset, briefer duration and frequently severer course. Currie states that repeated injections of horse-serum induce symptoms of supersensitiveness in man: also that the administration of the second of two injections, after the termination of the latent period of the first, may curtail the latent period of the second injection and that the length of the interval of time between the first and second injections is more essential.
Wright (1903) says that there are processes in immunization when the interval between administrations of the active substance has an important influence.

It is unfortunate from the point of view of this work that, in this case, we are dealing with an "accelerated" reaction, in consequence of which the incubation periods of the last two rashes cannot be accepted as typical of these types.

It is a noticeable feature of these latter two rashes that the incubation periods were 5 and 8 days respectively from the time of the second injection of serum and these periods are much shorter than the average periods for those two types of rash according to the results seen in Table V. They were also of briefer duration lasting 1 and 2 days respectively, and in the last one, i.e. the circinate type, there was much constitutional disturbance.

All these facts are in accordance with the statements of the observers quoted.

The point, however, to be brought out in connection with this case is that the whole three types of rash were observed in a single person and that these rashes followed one another in the order urticarial first, morbilliform second and circinate last.

The explanation of the occurrence of more than one rash in a single case is given by Goodall as being due to the mixing of the sera of two or more horses and he attributes both the frequency and the character of the rashes largely to the idiosyncrasy of the horse. He notes, in this connection, that different sera will produce different sera phenomena.

Similarly, Ker states that the blood of certain horses appears to be more liable to cause "serum disease" than that of others and Park & Bolduan say that the individuality of the serum may play a prominent part in the type of rash which is produced.
It is proposed, in Part III of this work, to deal with this question. It is here suggested, in view of the results obtained on investigation of the different types of rash, that the causes given above for the occurrence of different rashes, or, indeed, for the relative frequency of occurrence of the three types, may certainly be true but for more specific reasons than those offered by the various observers quoted.
B. A STUDY OF CASES RECORDED AS HAVING DEVELOPED SCARLATINIFORM OR DIFFUSE ERYTHEMATOUS SERUM RASHES.

<table>
<thead>
<tr>
<th>Consecutive Number</th>
<th>Incubation Period</th>
<th>Type</th>
<th>Duration of Rash</th>
<th>Temperature</th>
<th>Days of Occurrence after Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>Sc</td>
<td>2</td>
<td>99.8</td>
<td>15th. day</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>Sc</td>
<td>2</td>
<td>101.4</td>
<td>7th-10th. days</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>E</td>
<td>2</td>
<td>102.8</td>
<td>1st-10th. days</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>E</td>
<td>5</td>
<td>102</td>
<td>1st-14th. days</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>E</td>
<td>3</td>
<td>102</td>
<td>4th-5th. days</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>E</td>
<td>1</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>E</td>
<td>1</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>E</td>
<td>1</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>13</td>
<td>Sc</td>
<td>1</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>Sc</td>
<td>1</td>
<td>Nil</td>
<td></td>
</tr>
</tbody>
</table>

E - DIFFUSE ERYTHEMATOUS
Sc - SCARLATINIFORM

All the cases of the above type which were met with in this investigation number 10 (Table I).

As was previously suggested, it was thought that a study of these cases in detail might throw some light on the question whether Scarlatiniform and Diffuse Erythematous Rashes were in reality due to serum. As stated on page 6, this group was left out of consideration altogether because of the facts elicited concerning the reported cases. It was thought that the presence in a ward, synchronously with the presence of such a type of rash, of undoubted Scarlet Fever or other exanthemata might have an important bearing on the question.
The 10 cases have therefore been subjected to careful investigation and all the available information concerning them collected and at the same time the ward journals have been carefully scrutinised for the presence of Scarlet Fever or other exanthemata occurring in the wards in which these alleged serum rashes were observed, particular attention being paid to the incubation periods of the concurrent diseases.

It may be stated here that Scarlet Fever especially is very liable to break out in Diphtheria Wards due both to cases that are admitted as Diphtheria but prove to be Scarlet Fever, and, secondarily, to these new admissions, to cases already present in the ward becoming infected. Moreover it is no uncommon thing for a single case to show the presence of both diseases concurrently. In cases like these, the source of the Scarlet Fever is known definitely. Scarlet Fever, however, frequently crops up in a Diphtheria Ward, its origin not being known, as anyone familiar with isolation hospitals is well aware and, in consequence, Diphtheria Wards have frequently to be allowed to "run down," then disinfected before any other Diphtheria cases can be admitted.

Although some observers are dogmatic on the subject and state that such a type of serum rash may occur, there are a great many who are less confident and indeed some who flatly deny that such a type of rash is due to serum at all. There is not the same doubt regarding the other types.

Though the cardinal symptoms of Scarlet Fever are headache, vomiting and sore throat, these may not all be present and indeed none may be present in the milder types of the disease. The accompanying symptoms therefore are not of much value, unless when present.

There are cases recorded by other observers as serum rashes of this type and, although the diagnosis has been made carefully and after full investigation of each case,
nevertheless, the alleged serum rash proved to be Scarlet Fever after all.

Kellogg (1901), Oberwinter (1903) and v Rittershain (1902) have recorded cases, which were diagnosed as serum rashes of this type and in some of which the rash was first noticed near the site of injection, yet the diagnosis proved to be wrong, the condition being due to Scarlet Fever and not to serum. It must also be borne in mind that desquamation in mild cases of Scarlet Fever is frequently not very definite, depending more or less on the profuseness or otherwise of the rash.

In the following account of the cases met with in this work, it is regrettable that the information regarding one or two is meagre and scanty but, nevertheless, would appear to be sufficient for the purpose.

CASE I
Reported as Serum Rash of a Scarlatiniform type.
No symptoms noted. Temperature elevated for one day. Rash lasted two days. Present on trunk. No desquamation noted. No other concurrent infection in ward except that of German Measles some time later which probably had no relation to this case.

This case is one in which the information is very meagre. The important point with regard to it is that all the information available was drawn from notes made by the nurse. The Medical Officer in charge had made no note of this alleged serum rash.

In regard to all the other cases, the information given is taken from notes made by the Medical Officers in charge.

CASE II
Reported as Serum Rash of Scarlatiniform type.
Rash of diffuse nature on trunk and limbs. The accompanying symptoms were pain in the ear and an elevated temperature which lasted for four days. The rash lasted for two
days. The case subsequently developed otorrhoea and adenitis. No desquamation noted. Another case was removed from the same ward with typical Scarlet Fever 9 days after the appearance of this alleged serum rash.

CASE III

Reported as Serum Rash of Diffuse Erythematous type.
Rash present on chest, back, and limbs, well marked round site of injection. Rash lasted two days. Face flushed, pulse rapid, (144), temperature elevated for the first 10 days after admission.
Two cases in the same ward developed typical Scarlet Fever 2 days previous to the appearance of this rash.

CASE IV

Reported as Serum Rash of Diffuse Erythematous type.
Present on trunk and limbs. Rash lasted 5 days. Temperature elevated for the first 14 days after admission, adenitis on the right side of neck, and albuminuria and double otorrhoea present also.
This case was in the same ward as next case (V). Both cases developed the rashes on the same day.

CASE V

Reported as Serum Rash of Diffuse Erythematous type.
Rash generalised, lasted three days and accompanied by elevated temperature which lasted also three days.
In regard to both these cases (IV & V), a case of typical Scarlet Fever occurred in the same ward 3 days previous to the appearance of these alleged serum rashes. Another case of typical Scarlet Fever was removed from the ward 7 days previous. Other two cases were removed 8 days previous, one of these with Scarlet Fever and the other with desquamation.

CASE VI

Reported as Serum Rash of Diffuse Erythematous type.
Rash bright and generalised which disappeared quickly.
There was no temperature. The fauces were slightly congested. A case had been removed from the ward 12 days previous to the appearance of this alleged serum rash suffering from German Measles.

CASE VII

Reported as Serum Rash of Diffuse Erythematous type.

Rash generalised and lasted one day. There was no temperature. Three cases were removed from the same ward with German Measles: one day previous to the appearance of this alleged serum rash: one 9 days after and one 21 days after the appearance of this serum rash.

CASE VIII

Reported as Serum Rash of Diffuse Erythematous type.

Rash was not abundant, present on trunk, lasted for one day and there was no temperature.

A case of typical Scarlet Fever was removed from the same ward 12 days after the appearance of this alleged serum rash.

CASE IX

Reported as Serum Rash of Scarlatiniform type.

Rash was generalised but faint in character. It lasted one day and there was no temperature.

A case was removed from the same ward 3 days previous to the appearance of this alleged serum rash, having been found to be desquamating from Scarlet Fever.

Three other cases were also removed 8, 18 and 27 days respectively after the appearance of this rash suffering from typical Scarlet Fever.

CASE X

Reported as Serum Rash of Scarlatiniform type.

Rash was generalised, lasted one day and there was no temperature. The rash was followed by adenitis 3 weeks later.

Four cases were removed from the same ward with typical
Scarlet Fever 1 day previous and 7, 8 and 17 days after the appearance of the alleged serum rash.

In attempting to analyse these cases of alleged serum rashes it is carefully borne in mind that they have been recorded by observers (with the exception of Case I) highly competent in every way and well qualified to pass an opinion as to whether a rash was due to serum or not. It has, however, been already pointed out that others, after most careful diagnosis, have made mistakes and although perhaps it is easier to form an opinion with regard to a rash when it is actually under observation, nevertheless, the facts brought to light with regard to these cases appear to throw considerable doubt on their authenticity as serum rashes, so much so indeed in some cases that it is difficult to see why they were considered to be serum rashes at all.

Dealing with the cases individually it is not proposed to pass any comment on Case I except that the opinion of a nurse on the nature of a rash, no matter how competent she may be, is of no material value in a work of this kind and such a source of information has been for that reason almost entirely neglected. On the other hand it is considered to be quite legitimate to accept the statement recorded by a nurse that, e.g. joint pains were present. In Case II the presence of pain in the ear and subsequent development of otorrhoea and adenitis, coupled with the fact that Scarlet Fever occurred in the same ward 9 days afterwards is sufficiently significant, if not absolutely conclusive, that the rash was one of mild Scarlet Fever and not a serum rash.

In Case III the flushed face, rapid pulse and distribution of the rash, even though it was well marked round the site of injection, together with the presence in the ward of Scarlet Fever two days previously and the persistent high
temperature goes a long way to discredit this rash as being due to serum but makes it highly probable that it was due to Scarlet Fever.

In Case IV the rash was present on trunk and limbs, the temperature was elevated for a fortnight after admission, there was adenitis present at the time the rash appeared, albuminuria and discharge from both ears. The rash occurred on the same day as that of the next case (V) and in the same ward no fewer than 4 cases of Scarlet Fever occurred, one 3 days previous to the appearance of these serum rashes, one 7 days previous, one 8 days previous and one desquamating from Scarlet Fever 8 days previous. It is inconceivable that these two cases could have developed anything else but Scarlet Fever.

In Case VI the rash was bright and generalised and faded quickly, the fauces were slightly congested, there was no temperature and 12 days previously a case had been removed suffering from German Measles.

It is as likely as not that this case was suffering from German Measles.

In Case VII the rash was generalised, faded quickly and there was no temperature. No less than 3 cases were removed from the same ward suffering from German Measles. One a day previous, one 9 days after and one 21 days after the appearance of this rash, a train of circumstances that is highly suggestive of this alleged serum rash being in reality German Measles also.

In Case VIII the rash was not abundant, lasted only a short time and was accompanied by no temperature, nevertheless, typical Scarlet Fever occurred in the same ward 12 days later and it may be noted that the case showing the alleged serum rash had not of course been removed from the ward. It is very highly probable that this rash was one of Scarlet Fever and not due to serum.

In Case IX the rash was only faint in character and there was no temperature. Four cases of Scarlet Fever were
removed from the same ward, one desquamating 3 days previous and three 3, 18 and 27 days after the appearance of this serum rash, a sequence of events that makes the authenticity of this rash being due to serum extremely doubtful.

In Case X the rash which, though generalised, lasted only a day, was followed by adenitis three weeks later, a period at which it is common to get such a complication after Scarlet Fever. Moreover, no less than 4 cases of Scarlet Fever were removed from the same ward 1 day previous and 7, 8 and 17 days after the alleged serum rash occurred. It is improbable, if not impossible, that this rash was not due to Scarlet Fever also.

The important feature of all the cases quoted is the duration of their rashes. In the majority, the rash does not last long, probably not long enough to be properly observed. A Medical Officer in charge of a Diphtheria ward, when confronted by a rash, would naturally prefer that rash to be due to serum rather than to any of the exanthemata, otherwise his ward becomes closed and no more cases are received. His attitude is, therefore, probably one of delay until the rash has been under his own observation for a little longer and until he is certain of the diagnosis. In the meantime, however, the rash fades and, in consequence of the transient nature of the rash and the concomitant symptoms being absent or not present in typical form, he concludes that the rash has been due to serum and not to anything else. Desquamation moreover may be small in amount, of the "powdery" variety and not noticed. It is possible, if not highly probable, that these cases of alleged serum rashes were in reality cases of exanthemata of the very mild or "unrecognised" type. According to the information obtained with regard to the presence of other infections, each of the cases (except Case I) comes within the range or incubation periods of concurrent infections, and the association of this fact with the fact that the
occurrence of this alleged type of serum rash has been considered by others as uncertain tends to throw such considerable doubt on its claims as a type of serum rash as to challenge its authenticity or even to disprove it altogether. It is noted, also, in contrast to those of the other three types, that none of the cases were accompanied by any of the other symptoms of "serum disease" except, of course, pyrexia in a few of them. This point in itself is significant.

The number of cases of this type also that were observed is very few - 10 and it is rather suggestive that no case (except Case I) is entirely free from the possibility of infection with concurrent diseases. It would have been thought that, if this type were a genuine example of a serum rash, cases should be found where no concurrent infection was present and therefore where there was less suspicion and doubt, concerning them. None, however, occurred.

Moreover, no case showing this type of rash has been encountered by the writer which did not prove to be due to Scarlet Fever or other exanthemata and not to serum. The facts elicited in a study of these cases are considered to be sufficient evidence in support of an opinion that is inconsistent with the view that such a type of serum rash exists and, failing proof to the contrary, it is held that the Scarlatiniform or Diffuse Erythematous type of rash, encountered in relation to "serum disease" is in reality the exanthem of true Scarlatina or German Measles and has no claim to be considered to be due to serum.

In view of this conclusion this type was considered not to have any bearing on the special object of this work and was consequently omitted altogether.
In PART I of this investigation, it was found that there were three distinct varieties of "serum disease" and those three varieties differed from each other not only in the type, incubation periods, order of occurrence and duration of their respective rashes, which were perhaps the main differences between the three types but also in the frequency of occurrence of other symptoms of "serum disease," by which the rashes might be accompanied, such as pyrexia, joint pains, etc., and in the mildness or severity of these symptoms. It was also found that, where certain features were common to all three varieties of serum disease, these features differed in degree e.g. pyrexia is a feature that may be present with all three varieties but it was shown that pyrexia is very much more trivial with the urticarial type than with the other two, and, similarly, joint pains, though they may occur in all three varieties, are inclined to be more severe in the morbilliform type than in the other two.

In the Appendix to Part I the conclusion arrived at with regard to the Scarlatiniform or Diffuse Erythematous type of rash was that it was due to one or other of the exanthemata notably Scarlet Fever and not to horse-serum. The information to be obtained from a study of cases presenting more than one serum rash is of considerable importance. The number of such cases showing double rashes was very small compared to the number of single rashes - only 15. Two serum rashes developed in each of the 15 cases separated from each other by a definite interval of time and, in each, the second rash was always of a different type. It was observed that the primary rash in each case was of the urticarial type. The results obtained confirmed the observations previously made with regard to the order of occurrence of the rashes. It was obvious that the urticarial type at least develops sooner than the other
two in the same person.

No case showing the ordinary reaction was found in the present investigation which had developed more than two rashes, though it is conceivable such cases may occur, and indeed, the presence of three rashes in a single case has been noted by some observers.

There was, however, one case showing an "accelerated reaction" and presenting the three varieties of "serum disease." It was noted in this connection that the order of occurrence of these rashes was in conformity with previous results. Although in this case an abnormal reaction occurred, the sum of the evidence seems to favour the view that the three varieties may exist in a single person after a single injection of horse-serum but that they may manifest themselves in that person clinically at different times. It would appear, however, that such an occurrence is very uncommon and that even the presence of two rashes in a single case is also very much less frequent than the ordinary single rash.

Owing to the range of the incubation periods of the three varieties it is conceivable that two different rashes might appear at or about the same time. If such an event did happen it might explain the different appearances or so-called mixed rashes, alleged to have been seen in certain cases by some observers.

The conclusion to be drawn from the results obtained in this part of the investigation appear to show that there are three varieties of "serum disease" and that these varieties, though similar to each other in a general way, yet can each have a separate existence and differ so markedly from each other individually in the character of their manifestations as to leave little doubt that the three varieties are distinct and independent of each other and probably therefore produced by different causes: and, just as the three varieties of "serum disease" show a
certain general similarity, one might expect to find the three causal factors, while presenting a corresponding general similarity, yet also distinguished from each other by independence of action and capable of separate existence.
PART II

TO SHOW THAT THE PROTEINS OF NORMAL OR ANTITOXIC HORSE-SERUM ARE DISTINCT FROM EACH OTHER IN THEIR CHARACTERS AND ANAPHYLACTIC REACTIONS.

A. THE DISTINCTION IN CHARACTERS BETWEEN THE PROTEINS OF HORSE-SERUM.

B. THE PROTEIN-CONTENT OF ANTITOXIC OR NORMAL HORSE-SERUM.

C. ANAPHYLAXIS TO THE SEPARATED PROTEINS OF HORSE-SERUM AND TO OTHER PROTEINS.

D. THE PRESENCE OF PRECIPITINS IN THE BLOOD.
A. THE DISTINCTION IN CHARACTERS BETWEEN THE PROTEINS OF

HORSE-SERUM.

Blood is composed of corpuscles and plasma, and plasma contains a number of different proteins belonging to the class of coagulable proteins. No albumoses or peptones are present. Since the plasma in clotting gives rise to fibrin and serum, its protein constituents may be divided into those which are the precursors of fibrin and those which are still contained in the serum.

Fibrinogen is a globulin. Thrombokinase and thrombogen, which are involved in the production of thrombin, are phosphorous containing proteins probably belonging to the class of nucleo-proteins. These precursors of fibrin are converted on coagulation into fibrin and, in the production of antitoxin or normal horse-serum for clinical use, these proteins would have been eliminated.

The proteins which are still contained in the serum may be grouped according to Starling (1912) in two classes, namely, serum albumins and serum globulins. All the serum proteins are completely precipitated by saturation with ammonium sulphate. By half-saturation in this way the globulins may be precipitated and can be separated from the serum albumins by filtration. The proportion of globulins to albumins as ascertained by this method is known as the "protein quotient." This quotient varies in different animals.

The globulins of serum, known as para-globulin or serum globulin, are obtained by half-saturation with ammonium sulphate. Their solutions coagulate at about 75°C. Since globulin is insoluble in distilled water it is precipitated on dialysing serum against distilled water. The precipitate obtained in this way is not, however, so great in extent as that obtained on half-saturation and on this account the globulin fraction of the serum proteins has been divided into two fractions, namely,
euglobulin, precipitated by dialysis, and pseudo-globulin, not precipitable by dialysis but thrown down on half-saturation by ammonium sulphate. The globulins differ from the albumins of the serum in containing constantly organic phosphorous as an integral part of their molecule. Serum albumin remains in the serum after half-saturation with ammonium sulphate. It can be precipitated from this by complete saturation with ammonium sulphate or sodium-magnesium sulphate, or in the crystalline form by slight acidification as in Hopkin's method. Serum albumin is soluble in distilled water. Its solutions, therefore, can be dialysed without any precipitation taking place.

Although serum protein may be regarded as a complex unit and exists in serum probably in some manner combining all its varied colloidal constituents so as to form one labile mass of fluid protoplasm, still by simple means such as dialysis, dilution, or addition of salt, this unit can be broken up with the separation of the various proteins designated as serum globulin (eu- and pseudo-) and serum albumin.

Ledingham (1907), in his work on the relation of the antitoxin to the globulin-content of blood serum, makes similar statements. He says that the term "globulin" comprised two or more bodies having different salt precipitation limits as well as different antitoxin-contents. The hitherto accepted characteristic of serum globulin, in contra distinction to serum albumin, viz. its insolubility in salt-free water, was untenable because, after precipitation by dialysis of the typical insoluble globulin, there remained in solution a relatively much larger quantity of a proteid body.

Fuld & Spiro (1900) determined that by fractional precipitation of serum with ammonium sulphate two globulin fractions could be obtained, one precipitated by 28.33% saturation and the other only by 34.46% saturation. To the former fraction, precipitable by one-third saturation
hofmeister gave the name "euglobulin" and to the latter, precipitable only by half-saturation, the name "pseudo-globulin". The euglobulin had the power of coagulating milk, while the pseudo-globulin had a more or less pronounced inhibitory action on milk coagulation.

The division of globulin into two portions, euglobulin and pseudo-globulin, has been repeated by other observers and, although the division is a more or less artificial one from the purely chemical point of view, the remarkable differences exhibited by them in their capacity as antibody carriers proclaim a real duality and render it highly essential that this mode of division should be retained.
B. THE PROTEIN-CONTENT OF ANTITOXIC OR NORMAL HORSE-SERUM.

Ledingham, by means of experiments with horses, found that, during the immunisation of one horse which yielded an antitoxic serum of a high degree of potency, the percentage globulin-content of the total protein progressively increased, the increase affecting the euglobulin fraction more than the pseudo-globulin fraction whereas, during the immunisation of another horse which failed to yield an antitoxic serum of a high degree of potency, the globulin-content of the total protein showed no tendency to increase. The slight rise in total protein which did occur was due to an increase in the albumin fraction.

It is also shown that before immunisation, although two horses may have practically the same amount of total protein, the globulin fraction may preponderate enormously over the albumin fraction.

These experiments show that the amount of euglobulin, pseudo-globulin and albumin, present in the serum of horses, may vary to a slight extent in normal horses and to a greater extent in immunised horses especially susceptible animals. Different horses display different reactions to diphtheria toxin.

He states also that the protein ratio in the goat may vary. Schmidt & Schmidt (1917) state that the protein ratio varies considerably in different rabbits and to a somewhat lesser extent in individual rabbits.

Meyer, Hurwitz & Tanseig (1918) state that the percentage of serum globulins increases markedly during the course of immunisation of such animals as the horse, dog, goat and rabbit.

Serum, therefore, as used clinically whether normal or antitoxic may contain varying quantities of the three proteins euglobulin, pseudo-globulin and albumin. Ledingham has further shown by experiments that the pseudo-globulin fraction of serum in the horse contains the
greater part, if not all, the antitoxin, this relationship holding good, however, only when the antitoxin-content of the serum is steadily rising, confirming thereby the similar results of Pick.
C. ANAPHYLAXIS TO THE SEPARATED PROTEINS OF HORSE-SEUM, AND TO OTHER PROTEINS.

According to the theory of Vaughan (1907) and later of Biedl & Kraus (1911), Freidberger (1913), Pfeiffer (1913), Schittenhelm & Weichardt (1912) and others the production of the anaphylactic poisons depends on a splitting of protein.

Auer & Van Slyke (1913) have found the cleavage products of proteins in the blood of animals at the moment of the anaphylactic reaction.

Doerr & Russ (1909), working with guinea-pigs and using separated proteins of horse-serum, found that the euglobulin fraction exhibited the maximum activity, the albumin being practically inert and the pseudo-globulin occupying an intermediate position.

The anomaly here is the failure of the albumin fraction to act as an anaphylactic antigen. The cause of this failure is cleared up by Dale & Hartley (1916) in their work on anaphylaxis to the serum proteins.

These observers are quite clear on the point that every sensitisation with a whole serum is in reality a complex multi-sensitisation and that, in any attempt to investigate the nature of the antigenic difference, it is essential to work with individual pure proteins.

Using specimens of the three serum proteins euglobulin, pseudo-globulin and albumin, prepared by them in as pure a state as ordinary methods of detection and separation could discover, these observers come to the conclusion that each of the three proteins separable from horse-serum by their physical and chemical properties can act as an anaphylactic antigen. Sensitisation with euglobulin produced a more clearly specific sensitiveness than that with either of the other proteins. They attribute the failure of albumin to act as an anaphylactic antigen, as noted by Doerr & Russ, to the fact that the sensitiveness of the
guinea-pig to albumin is later in development than to the globulins particularly when whole serum is used containing all three proteins, and they consider that this lack of apparent sensitiveness may be due to genuine desensitisation or to an excess of antibody in the blood.

The impression that there is a considerable community of antigenic function among the proteins of one serum, is not in their view justified but it is held to be disproved by the effects of sensitising by the separate proteins instead of by whole serum and also by the effects of desensitisation. A guinea-pig which has received a sensitising injection of one of these proteins is more sensitive to that one than to either of the others from the same serum. It was also shown that an effective dose of any of the proteins, to which the guinea-pig's muscle has been sensitised, partially or completely desensitises it to the other proteins of the same serum. They regard any overlap of antigenic function as due to incomplete separation as they found it appeared most prominently when the impurity of the sensitising protein was most likely to be considerable and the results obtained by them were in accordance with this view: the sharpest distinction was found to be between euglobulin and albumin and each of these can be obtained almost certainly uncontaminated with each other, and though the distinction in regard to pseudo-globulin was not so definite, yet it is deemed by them sufficient to conclude that the different proteins of a serum, in so far as they can be obtained pure from one another, can act independently as anaphylactic antigens. Thus immunological "specificity" is narrowed down to a discrimination between the different pure proteins of a single tissue of one species.

The amount of protein needed to evoke some degree of sensitiveness is almost inconceivably small.

An analysis of the separated proteins from horse-serum gives ground for belief that the antigenic character
of each protein molecule may depend on the pattern of the structure of the molecule and the order of amino-acid linkage.

Wells & Osborne (1913, 1915), working with hordein from barley, glutenin from wheat and gliadin from both wheat and rye, conclude that the specificity of the anaphylaxis reaction is determined by the chemical structure of the reacting proteins rather than by their biological origin. They give numerous instances in which the different pure proteins from one plant species act as separate antigens and animals sensitised with two proteins will react with either.

According to Wells (1909) there are marked differences in the anaphylaxis reaction in different animals, and there seems to be differences in the reactions produced by different proteins.

Rosenau & Anderson (1907) state that guinea-pigs may be sensitised to three strange proteins - blood-serum, egg-white and milk - at the same time. The hyper-susceptibility to each protein substance is manifested by a second injection of the corresponding protein. The three reactions are as distinct and specific as three separate infectious diseases. They believe that chemical changes lie at the basis of this reaction.
In regard to the question of the presence of precipitins in the blood of persons suffering from "serum disease," Hunter (1905) found that each of the serum proteins, euglobulin, pseudo-globulin and albumin, was capable of exciting precipitin formation and that the precipitin obtained in each case reacted most strongly with the protein used in its production.

Wells (1915) states that the amount of precipitin in the blood of persons injected with anti-diphtheritic horse-serum is not dependent on the amount or lot of anti-toxic serum administered or on the age, sex or weight of the patient, nor is it's duration in the patient's serum. The amount and possibly the duration of precipitin in the blood are dependent on some, as yet unknown, intrinsic process of the organism, which, however, is initiated or activated by the introduction of foreign protein in the antitoxic serum.

There is no evidence in his series of cases to indicate that the length of the incubation period of the precipitin element is influenced materially by the quantity or method of administration of the antitoxic serum.

Precipitin is utilized or withdrawn from the blood during the course of "serum disease" and possibly is a factor in the production of the various phenomena of "serum disease."

According to Joachimoglu (1911), it also disappears instantly with anaphylactic shock.

Experimentally, Bulger (1916) has shown that the precipitate from a precipitin reaction will cause digestion in the normal serum and this takes place with very small amounts of precipitate. He states that digestion is due probably to the removal of antiferment, allowing the protease, which is always contained in serum and which is normally prevented from acting
by this antiferment, to act on the serum proteins. The amounts of protease and antiferment seem to vary greatly under different conditions.

He also states that, possibly in anaphylaxis, the antiferment being removed, the serum proteins are exposed to the action of the protease with toxic split products as a result. He notes also that, experimentally, maximal digestion occurs only with certain quantities of precipitate, larger or smaller quantities causing less digestion.

Kritchewsky (1918) shows, by means of experiments that the sap of the plant - Cotyledon Scheideckeri, which is able to precipitate animal serum, has the power to provoke symptoms and changes characteristic of and indistinguishable from those of "anaphylactic shock", when introduced into the veins of animals.
SUMMARY OF PART II

The conclusions to be drawn from the statements and results of experiments of all these observers may now be summarised thus:- horse-serum whether normal or antitoxic, as used clinically for therapeutic purposes, contains three proteins, euglobulin, pseudo-globulin and albumin; these three proteins differ from each other in the length of time required for their precipitation by ammonium sulphate and the distinction between the three proteins depends probably on the chemical structure of the molecule of each.

The amount of each protein present in horse-serum is a variable quantity, especially so in antitoxic serum where there may be a considerable preponderance of one over the others.

Anaphylaxis depends on the introduction into the body of a foreign protein and on the production of a poisonous substance produced by the reaction between the body cells and the cleavage products of the foreign protein.

Each of the three proteins of horse-serum can act as an anaphylactic antigen.

The amount of protein required to produce some degree of sensitiveness is almost inconceivably small.

The anaphylactic reactions of the three proteins of horse-serum are distinct from each other both as regards sensitisation and desensitisation and also in the length of time required for the production of the reactions. The anaphylactic reactions are in some cases specific and the specificity of the reaction is greatest when the separated protein is purest.

The specificity of anaphylactic reactions with proteins is not confined to the separated proteins of horse-serum but has also been noted with other proteins.

Each of the proteins of horse-serum is capable of exciting precipitin formation in the blood in "serum disease." This precipitin formation is related in some way to the presence
of "serum disease" as it is found to disappear from the blood during the course of "serum disease."

Experimentally, in relation to the production of anaphylaxis in animals, the precipitins cause an immediate mobilisation of non-specific protease in varying amounts and this is made possible by the removal of the antiferment. By the action of the protease on the serum proteins, cleavage products are formed and these split products are the main agents concerned in the causation of anaphylaxis.
PART III

TO ATTEMPT TO CORRELATE SPECIFICALLY THE VARIOUS FORMS OF "SERUM DISEASE" WITH THE VARIOUS PROTEINS OF HORSER-SERUM.

A. THE RELATION BETWEEN ANAPHYLAXIS AND "SERUM DISEASE".

B. THE SPECIFIC CORRELATION OF THE VARIOUS FORMS OF "SERUM DISEASE" WITH THE VARIOUS PROTEINS OF HORSE-SERUM

C. CONCLUSIONS
A. THE RELATION BETWEEN ANAPHYLAXIS AND "SERUM DISEASE"

Anaphylaxis is a word that was coined by Richet (1913) in 1902 to describe the peculiar attribute which certain poisons possess of increasing instead of diminishing the sensitivity of an organism to their reaction. It is the opposite condition to protection or phylaxis. In the first detailed description of the phenomenon, the basis of anaphylaxis was stated thus:—"a substance, which neither killed nor sickened a normal animal, gave rise to intense and fatal effects in an animal which some time previously had been given a dose of the same substance". The phenomenon had been noted before by other observers notably Koch in his work on tuberculosis and the name used by him was "supersensitiveness".

There can be doubt that anaphylaxis may occur in the human subject in connection with the use of sero-therapeutic injections. Such symptoms as fainting fits, coma, asphyxia and death may occur and have indeed been observed after the second injection of therapeutic serum and there is no doubt that these symptoms are the phenomena of true anaphylaxis. These symptoms are not, however, the symptoms which occur in the condition known as "serum disease"; although this disease occurring after two injections of serum in the form of "immediate" or "accelerated" reactions is much more severe than in the ordinary "mild" reaction after one injection of serum. The symptoms manifested in all the reactions are essentially the same but differ in degree of intensity.

Anaphylaxis in animals is obtained by injecting into the animal first a preparatory dose of the substance, and then, after a certain interval of time, a second or exciting dose of the same substance. Just as anaphylaxis occurs after these two injections in animals, so it has been found that it may occur after two injections of serum in man sometimes with fatal results. "Serum disease"
on the other hand, may occur also after the first injection of serum.

Most observers are agreed and there would appear to be no doubt that there is some relation between the two conditions - "serum disease" and anaphylaxis. Indeed "serum disease" is sometimes referred to as "serum anaphylaxis." Richet says that the symptoms of serum disease are directly comparable to the symptoms of anaphylaxis in animals.

It is suggested here that "serum disease," occurring after one injection of serum, would be directly analogous to any symptoms that might occur in an animal after the first or preparatory dose of an anaphylactising substance. No symptoms, however, have been noted as occurring in animals after the first or preparatory dose. It is possible that the lack of symptoms in the animal may be due to the inconceivably small dose required as the preparatory dose. There would, moreover, appear to be a disparity between the amount of the preparatory dose of protein injected into animals and the amount of protein present in the dose of serum injected into man for therapeutic purposes. The reason, on the other hand, may be that man displays a much more intense sensitivity to the injection of anaphylactising substances than does the guinea-pig for example, or other animals. In other words "serum disease" is a phenomenon peculiar to man and may be the clinical manifestation of the result of the first or preparatory injection of an anaphylactising substance.

After one injection of serum, there is produced in man, after an interval of time, a certain state the effects of which in certain cases may be manifested clinically by a train of phenomena known as "serum disease;" the reaction being in these cases generally mild, and further, man becomes a potential subject of anaphylaxis, so that, after a second injection of serum, anaphylaxis may occur, just as it does in animals, either in moderate degree accompanying the second attack of "serum disease" or in intense and
fulminating degree in the form of coma, dyspnoea, muscular weakness, syncope, asphyxia or death - "anaphylactic shock."

It is possible that "serum disease" is a clinical manifestation or by-product of a stage in the production of anaphylaxis and that a clinical and experimental study of the disease and a more extensive knowledge of its mode of production might furnish valuable information for the further elucidation of anaphylaxis.

It has been already noted that the injection of foreign proteins into animals causes anaphylaxis and so also the protein contained in therapeutic serum has been shown to be the responsible factor in causing to be produced the condition known as "serum disease."

Although the exact relation, experimentally, between "serum disease" and anaphylaxis is still wrapped up in considerable obscurity, the relation, theoretically, between the two conditions may appear to be sufficient as to allow of the mode of production of the one being compared to the mode of production of the other. If such comparison is permitted, then the statements and results of experiments of the various observers quoted in Part II on the production of anaphylaxis in animals can be applied to the production of "serum disease" in man.
B. THE SPECIFIC CORRELATION OF THE VARIOUS FORMS OF "SERUM DISEASE" WITH THE VARIOUS PROTEINS OF HORSE-SERUM.

It has been shown that there are three different forms of "serum disease." It has also been shown that there are three varieties of proteins contained in antitoxic or normal horse-serum. It has furthermore been shown that these three proteins are almost specific in their anaphylactic reactions in animals. It is conceivable, in view of the fact that it is known that the production of "serum disease" depends on the introduction into the body of foreign proteins, that these three proteins are responsible for the production of the three varieties of "serum disease.

The only proof that would be absolutely conclusive in support of this theory would be to inject into the human subject the separated proteins of horse-serum and study the effects. That mode of procedure, however, is quite out of the question, but the same result can be attained, if the anaphylactic reactions in animals of the three proteins are compared to the three clinical varieties of "serum disease" in man. Then it will be seen that there is a remarkable analogy between the effects in animals and the manifestations in man of those two conditions. The anaphylactic reactions on the one hand and the clinical varieties of "serum disease" on the other hand are so distinct and "specific" that the analogy can be explained satisfactorily only on the supposition that each of the three proteins acts specifically in the human subject by producing, each of them, a different variety of the phenomenon known as "serum disease!"

A point already noted was the greater frequency of occurrence of "serum disease" with the use of unconcentrated serum. Conversely the remarkable feature of the use of concentrated serum was the almost total elimination of urticarial rashes. By the concentration of serum the euglobulin and albumin fractions are in great measure removed, the pseudo-globulin
being left, as it was found to be concerned with the antitoxic principle of the serum. In the anaphylactic reactions in animals, euglobulin showed more clearly specific sensitivity and after a shorter interval of time than did pseudo-globulin or albumin. For these reasons, therefore, euglobulin might theoretically be correlated with the production of the urticarial form of "serum disease." On the other hand the longer interval of time required for its anaphylactic reaction suggests that albumin might be correlated with the production of the circinate form of "serum disease," pseudo-globulin being in this way left to be correlated with the production of the morbilliform type. This reasoning is of course purely theoretical and it is rather difficult to see how the theory could be substantiated by experiment and, although the correlation, as suggested, of "protein" with "variety of disease" may not be accurate, it is possible that the theory remains true although the suggested arrangement may be wrong.
C. CONCLUSIONS.

A comparison having been made of the results obtained in a study of "serum disease" (Part I) with the analogous results of the anaphylactic reactions of the proteins of horse-serum (Part II), the drawing of certain conclusions therefrom would appear to be justifiable.

1. The introduction of a foreign protein into man may cause it to act as the first or preparatory dose, necessary (as in animals) for the production of anaphylaxis and setting up thereby a state of "potential anaphylaxis," so that after a second dose the anaphylactic reaction occurs as happens in animals. Besides having this action, foreign proteins may, in some cases, cause certain clinical manifestations which are known, in relation to the therapeutic use of serum, as the phenomena of "serum disease" of which there are three varieties. Horse-serum, as used for therapeutic purposes and which contains variable quantities of the three serum proteins, may, after one injection, set up in the human subject certain changes of the nature of an intoxication with a poison, which may be produced by the action of a certain body (protease) on the foreign protein with the resulting formation of split-products and the ultimate production of a poisonous substance.

2. The three proteins of horse-serum (euglobulin, pseudoglobulin and albumin) may be the main agents in the production of three poisons, each of which may cause a different one of the three forms of the disease.

3. The non-appearance of "serum disease" after one injection of serum may be due to the fact that the three proteins introduced into the body are present in certain quantities in a certain ratio to each other or that the combining body (protease) or precipitins are not present in sufficient quantity.
4. The appearance of "serum disease" after one injection may be, conversely, due to the fact that there is present an excess, over a certain ratio, of one or more of the three proteins which have been introduced into the body; the delicate colloidal protein balance in the blood is therefore upset; and, in the process of righting this balance, the blood acts upon the excess of protein in the way already described, with the resulting formation of one or more poisons and the production of the corresponding variety or varieties of "serum disease."

5. The fact that the protease is non-specific and that precipitins, though they may be specific, are produced in every case makes it much more likely that the appearance or non-appearance of "serum disease" may depend on the amount of each of the three proteins introduced into the body and in consequence on whether the protein balance in the blood is upset or not rather than on the action of the combining body or precipitins. In other words the specific agents in the production of the disease may be the three proteins - euglobulin, pseudo-globulin and albumin.

6. The association of a particular batch of serum with the appearance of a certain type of "serum disease," as noted by some observers, may be due to the fact that the serum may contain an excess (over a certain ratio) of the corresponding protein. Thus the relative frequency of occurrence of the different types of the disease may be of no particular significance, depending, as it may do, on the amount of each protein present. It is therefore not surprising that there should be great diversity of opinion on this point by various observers and, as a matter of fact, there has been, as noted before.
7. Although such divergence of opinion exists regarding the relative frequency of occurrence of the three types of the disease, there would seem to be some ground for the belief that the urticarial type is apt to occur more often than the other two. This may be due to the fact that antitoxic serum is more frequently of "high grade" type, in which, according to Ledingham, there is an increased production of globulin over total protein and it has already suggested that euglobulin should be correlated with the urticarial type of the disease.

8. The three poisons, formed from the three proteins or their cleavage products, may be produced not all at the same time but at more or less different times, in this way accounting for the order of occurrence of the three types of serum disease as noted in Part I. The periods of production are not, however, absolutely distinct from one another but cover a certain range or interval of time which corresponds to the interval between the minimum and maximum incubation periods of the corresponding three types of "serum disease".

9. The quicker appearance of the disease after two injections of serum may be due to the fact that the combining body (protease) has been formed after the first injection and is, at the time of the second injection, already present in the body and its action on the proteins with the formation of split products is thereby hastened. The more severe nature of the disease after two injections of serum may be due to the fact that the reaction produced is accompanied by a moderate degree of anaphylaxis and that fatal results such as have been recorded as occurring after two injections are due, as in animals, to anaphylaxis in more intense and fulminating form viz. anaphyalctic shock.
These conclusions are mainly, of course, theoretical and would, as absolute proof that they were correct, require to be substantiated by further experimental evidence. An investigation of "serum disease" however, in as much as it is a disease of man and not, apparently, of animals, is more or less limited by the available methods of study. Nevertheless, the conclusions arrived at by means of clinical investigation and theoretical analogy would appear to be sufficient to indicate that "serum disease" bears the same relation to its three types as does serum protein to its three forms. A comparison may be found in the three varieties of a species and, as it has been shown that serum protein is the main causal factor concerned in the production of "serum disease," it is not a very great step further to correlate each of the forms of the one with a different type of the other. The results of this investigation, moreover, would appear to be of considerable importance in as much as the symptoms of the acute infectious diseases may be comparable to those of "serum disease" and may depend on similar phenomena, and that, therefore, a more extensive knowledge of the latter, such as this work has attempted to give, is desirable and indeed essential not only for the further elucidation of anaphylaxis but even for the comprehension of some of the most common phenomena of clinical medicine.
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