AN INVESTIGATION

INTO

THE PHENOMENA OF "SERUM DISEASE":

THE RELATION BETWEEN

ITS VARIOUS FORMS

AND

THE PROTEINS OF hORSE-SERUM.

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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.

A. THE TOXIC EFFECTS IN MAN OF INJECTIONS OF ANTITOXIC OR

NORMAL HORSE-SERUM ("SERUM DISEASE").

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 fre-

quently does not follow.

It was early noted, however, (Lublinski, 1894)[1] that in-

jections 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 antidiphtheritic 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.[2] 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 (1916)[3]

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 antimicrobic

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 experiment-ally by Johanessen (1895)[4] who found that the same phenomena were produced with normal horse-serum. Hartung (1896)[5] 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[6] 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 v Pirquet and Schick (1905),[7] 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.

(11) A rise of temperature showing that the rest of the body is taking part in the reaction.

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

(1V) Joint pains which are regarded as one of the most prominent symptoms. They bear some resemblance to an attack of rheumatic fever.

(V)   Enlargement of lymphatic glands in various parts of the body.

(V1) Oedema of loose tissues, generally of a slight nature and demonstrated by its being visible or by increase in the body weight.

(V11) 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)[5]

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)[8] states that it is contagious and believes it

to be true scarlatina and others that it is frequently limit-

ed 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.

P A R T   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 frequent-
ly on the extensor surfaces of the extremities though the
trunk may be involved also. The conjunctivae may be in-
jected and the eyelids puffy and, if the eruption is pres-
ent 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 cresentic 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.

S U M M A R Y

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 differ-
ent 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

	Number of Cases	Number of Rashes
GROUP A Type not stated	121	121

GROUP B
 	
    Type Scarlatiniform or
    Diffuse Erythematous
	10	10

GROUP C Accelerated Reactions	18	23

GROUP D
 	
    Type Urticarial, Morbilliform,
    Circinate
 	
Occurring after one injection of
 Serum
	266	281

Totals,	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 df 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 dealt with in detail in the Appendix. They were 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.[9]

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.

TABLE   II

GROUP D	Number of Cases	Number of Rashes
Type Urticarial, Morbilliform, Circinate		
1. Cases having one rash present	251	251
2. Cases having two rashes	15	30
Total,	266	281

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.

TABLE   III

TYPE	NO.	%	RATIO
Urticarial	218	77.6	10½
Morbilliform	42	15	2
Circinate	21	7.4	1
Totals,	281	100	

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.[10]   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 common-
est 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 warrant-
able 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)[11] 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)[12] 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[11] 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, through-
out 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" mani-

fests 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 IV

1	2	3	4	5	6	7
No. of Days after Injection of Serum	TOTAL CASES					
	Number			%		
	U	M	C	U	M	C
1						
2						
3						
4	9	1		4.1	2.4	
5	9			4.1		
6	18			8.3		
7	39	1		18	2.4	
8	34	1		15.6	2.4	
9	26	2		12	4.8	
10	23	4		10.5	9.5	
11	18	3	2	8.3	7.1	9.5
12	18	6	2	8.3	14.2	9.5
13	10	5	4	4.5	12	19
14	5	10	2	2.3	24	9.5
15	7	3	7	3.2	7.1	33
16	1	6	2	.4	14.2	9.5
17			1			5
18	1			.4		
19			1			5
Totals,	218	42	21	100	100	100

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 con-
sideration 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 in-
crease 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   V

Incubation Periods in Days	U	M	C
Minimum	4	4	11
Maximum	18	16	19
Average	9	12	14

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 con-
clusions 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 differ-
ent 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.
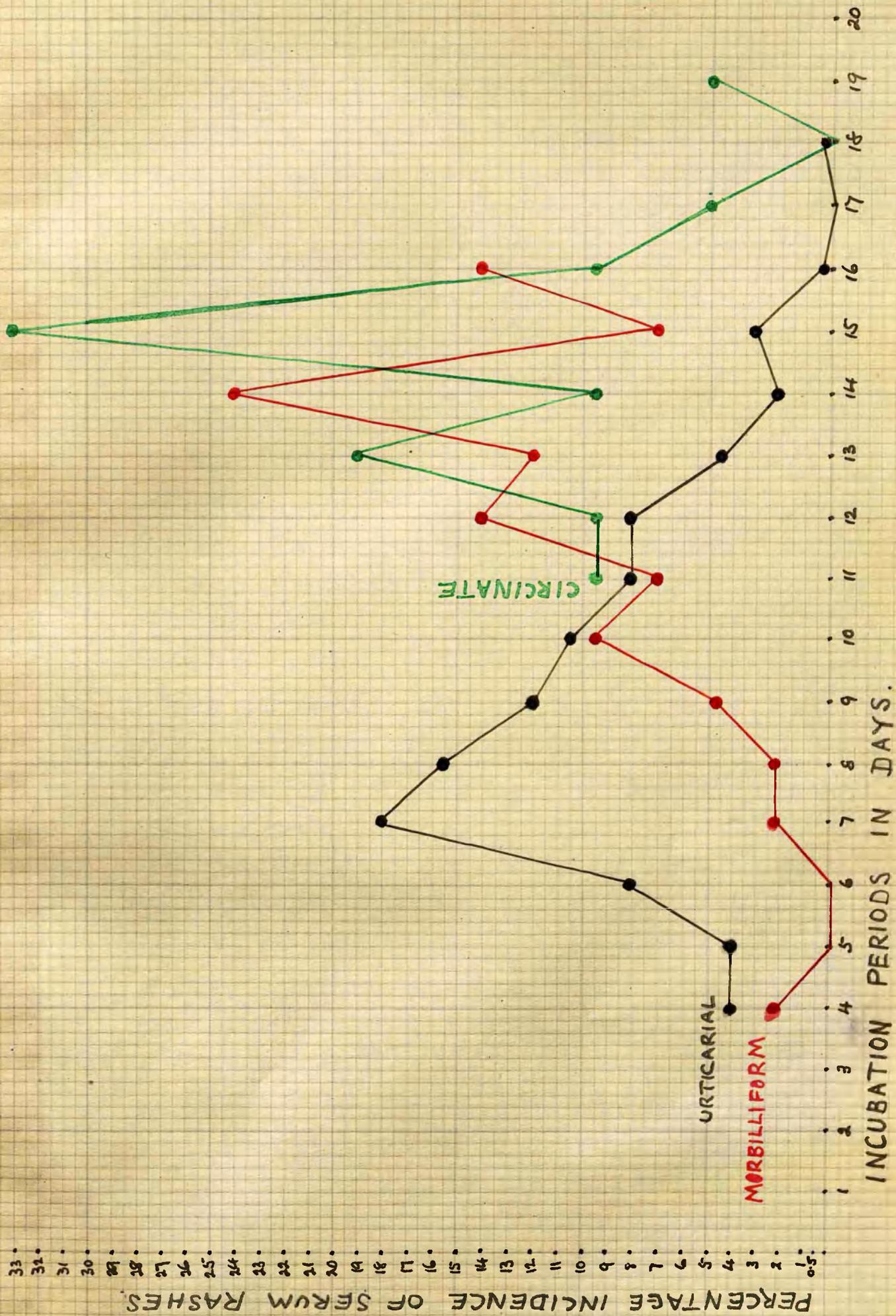
It will be seen from the graph, perhaps even more clearly
than from the table, the distinct difference between the
three types.

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 morbilli-
form 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 alternate-
ly, e.g. between 12th. and 13th. days the curve of the
morbilliform type descends whereas the curve of the circin-
ate 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 great-
est 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 percent-
age 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.
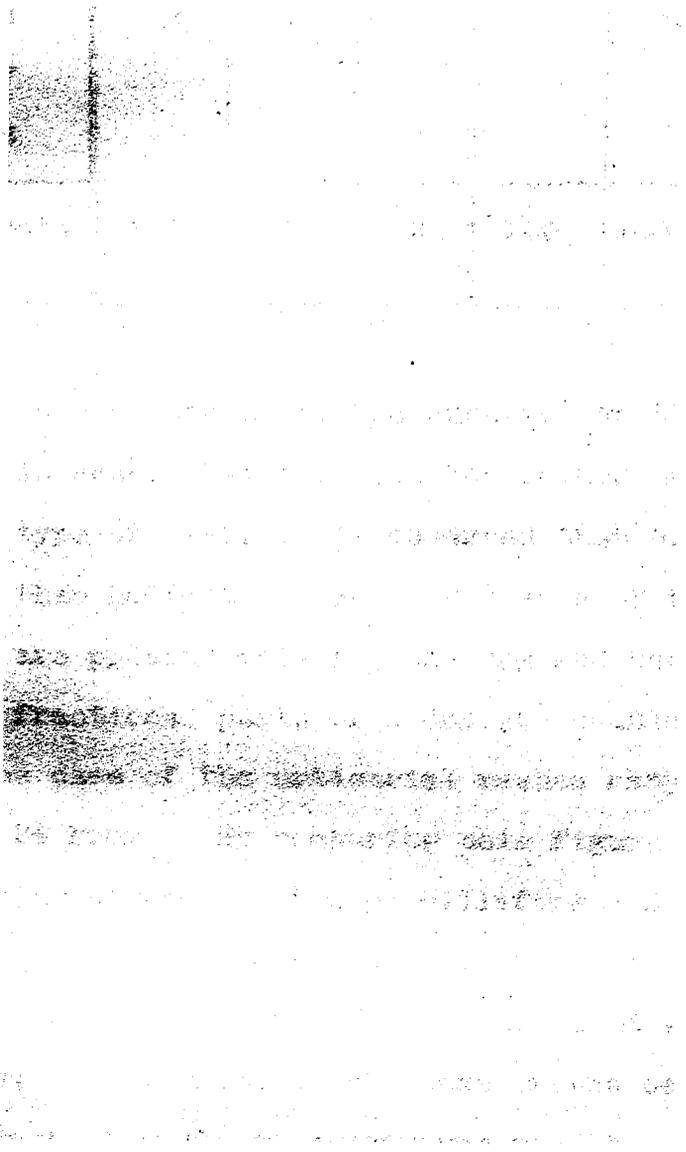
2. Duration of Serum Rashes.

TABLE   VI

No. of Days	TOTAL CASES					
	Number			%		
	U	M	C	U	M	C
1	111	9	5	51	21.4	23.7
2	58	18	10	26.6	43	47.6
3	28	11	3	12.8	26.1	14.2
4	15	3	2	6.9	7.1	9.5
5	4			1.8		
6	2	1		.9	2.4	
7						
8			1			5
Totals	218	42	21	100	100	100

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 corre-
sponding 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% respect-
ively. 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 morbilli-
form 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.

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

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

Temperature	TOTAL CASES					
	Number			%		
	U	M	C	U	M	C
None	174	12	3	79.8	28.6	14.2
※(A) elevated but accompanied by other symptoms	29	21	9	13.3	50	42.9
(B) elevated no other symptoms	15	9	9	6.9	21.4	42.9
Totals,	218	42	21	100	100	100

According to Ker[10] 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 compris-
es 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 79.8% 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 tempera-
ture 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, how-
ever, 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 gener-
al 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   VIII

Height of Temperature	U	M	C
Minimum	99	99	98.8
Maximum	103.4	104	103.6
Average	100.8	102	101.4

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 morbilli-
form 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 show-
ing 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 V Pirquet and
Schick[7]. Axenow (1914)[13] 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

No. of Days	TOTAL CASES					
	Number			%		
	U	M	C	U	M	C
1	8	5	3	53.4	55.6	33.4
2	5	2	1	33.3	22.2	11.1
3			2			22.2
4	2	1	2	13.3	11.1	22.2
5		1	1		11.1	11.1
Totals,	15	9	9	100	100	100

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 rash-
es and longest in cases having circinate rashes, thus bear-
ing out the results found in Table VI viz., that the con-
stitutional 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.

NUMBER AND PERCENTAGE OF TOTAL CASES WHICH DEVELOPED
OTHER SYMPTOMS OF "SERUM DISEASE".

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 re-
corded 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

SYMPTOMS	% Of Total Cases (4381)	% Of Total Rashes (281)	Number			%		
			U	M	C	U	M	C
Joint Pains	1%	18%	26	17	8	12	40.5	38.2
Oedema	½%	7-8%	17	4	1	7.7	9.5	5
Albuminuria			1			0.4		
Enlarged Glands	½%	5%	7	6	1	3.2	14.2	5

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[5] (6.7%) v Pirquet & Schick[7] (1%) Barbier (1904)[14] 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 fre-
quently 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 corre-
spond 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 disappoint-
ing 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 $\frac{1}{2}$% 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 fair-
ly 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 demon-
strable 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 obsefved.

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 along-
side 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 water-logging 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 obcur 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.[10]

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 [10] 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 find-
ings moreover have a distinct bearing on the special object
of this work.

TABLE   XI

Increase in the Cardiac Dullness	Total Number	%	Number			%		
			U	M	C	U	M	C
Present	36	72	29	4	3	80.5	40	75
Not Present	14	28	7	6	1	19.5	60	25
Totals,	50	100	36	10	4	100	100	100

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 consider-
ably 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 con-
siderably those of the urticarial and circinate. The
figure in the second row of the circinate column is slight-
ly 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

AMOUNT OF INCREASE	U				M				C			
	TRANSVERSE DIAMETER	LEFT BORDER	RIGHT BORDER	UPPER BORDER	TRANSVERSE DIAMETER	LEFT BORDER	RIGHT BORDER	UPPER BORDER	TRANSVERSE DIAMETER	LEFT BORDER	RIGHT BORDER	UPPER BORDER
No change		2	12	15			2	2			2	2
1/8"	3	2	4									
1/4"	3	6	2						2	2	1	
3/8"	2	2	1									
1/2"	9	6	2		1	1				1		
5/8"		3										
3/4"	3				1	1			1			
1,1/8"	1											
3rd. Space to 3rd. Rib				3								
4th. Space to 3rd. Rib				1								1
3rd. Space to 4th. Rib				2								
No Measurements Given	8	8	8	8	2	2	2	2				
Totals,	29	29	29	29	4	4	4	4	3	3	3	3

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 in-
crease was found to be as much as 1 and 1/8th. inch in one
case but the most frequent increase was $\frac{1}{2}$ 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 $\frac{3}{4}$ inch and $\frac{1}{2}$ inch.

As regards the right border 12 cases showed no change, the
maximum increase was $\frac{1}{2}$ 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),[16] 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 caridac 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 [16] is usually
seen in the ventricle when the muscular walls become in-
creased in thickness in order to overtake constantly re-
curring 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 pres-
ence 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 XIII

	U	M	C
1. Joint Pains	21	12	7
2. Oedema	13	1	
3. Enlarged Glands	4	2	1
4. Joint Pains & Oedema	3	2	1
5. Joint Pains & Enlarged Glands	2	3	
6. Oedema & Enlarged Glands	1	1	
Total Number	44	21	9
%	20.2	50	42.8

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 various 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 frequent-
ly 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 fre-
quently present when the cases are those in which a morbilli-
form 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 (accord-
ing 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 hav-
ing 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 temper-
ature 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

Consecutive Number	Incubation Period of Rash after Serum in Days	Type	Duration in Days	Maximum height	TEMPERATURE Day of Occurrence after Serum	Other Symptoms Present
1	10 14	U M	1 3	Nil 102.6	15th-17th days	Oedema & Joint Pains
2	10 16	U M	1 2	Nil 102	15th-17th days	
3	8 12	U M	1 3	Nil 102.6	11th-15th days	
4	9 15	U C	3 2	Nil 100.6	15th-16th days	
5	7 13	U C	2 1	Nil 102	11th-15th days	
6	9 15	U C	2 2	Nil 103.4	13th-16th days	
7	9 16	U C	1 1	Nil 100.8	13th-17th days	Joint Pains
8	7 13	U C	1 2	Nil 100	13th-14th days	Joint Pains
9	8 16	U M	1 2	Nil 101.6	15th-17th days	Joint Pains
10	13 16	U M	1 1	Nil 101.4	16th day	Joint Pains
11	7 15	U C	2 2	Nil 101	15th day	Oedema & Joint Pains
12	8 12	U M	2 1	Nil Nil		
13	4 13	U M	1 3	Nil 99.2	15th day	Joint Pains
14	11 14	U C	2 3	Nil 99.4	15th day	Joint Pains
15	6 10	U M	1 2	Nil Nil		

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.[11]   he gives 4 examples
of cases in each of which a single injection was follow-
ed 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 sufficient-
ly 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 dis-
appeared 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 Arthus[9], 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[9], 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[7] 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[9] 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

to the phenomena than the administration of serum in large doses.

Wright (1903)[17] 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[11] 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[10] states that the blood of certain horses appears to be more liable to cause "serum disease" than that of others and Park & Bolduan[12] 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   XV

Consecutive Number	Incubation Period	Type	Duration of Rash	TEMPERATURE	
				Maximum height	Days of Occurrence after Serum
1	14	Sc	2	99.8	15th. day
2	7	Sc	2	101.4	7th-10th. days
3	2	E	2	102.8	1st-10th. days
4	9	E	5	102	1st-14th. days
5	4	E	3	102	4th- 5th. days
6	7	E	1	Nil	
7	9	E	1	Nil	
8	9	E	1	Nil	
9	13	Sc	1	Nil	
10	5	Sc	1	Nil	

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 any-
one 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),[18] Oberwinter (1903)[19] and v Rittershain
(1902)[20] 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. T° 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 accompany-
ing symptoms were pain in the ear and an elevated tempera-
ture 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 over 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 a 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 con-
sidered 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 occurr-
ed 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 re-
moved 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, neverthe-
less, 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 prev-
ious and three 8, 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 aftre 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 dura-
tion 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.

S U M M A R Y   O F   P A R T   I

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 sever-
ity 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 present-
ing 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 separat-
ed 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.

P A R T   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) [21] 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 sodio-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),[22] in his work on the relation of the anti-toxin 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 precipita-tion by dialysis of the typical insoluble globulin, there remained in solution a relatively much larger quantity of a proteid body.

Fuld & Spiro (1900)[23] determined that by fractional pre-cipitation 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 "<u>euglobulin</u>" and to the latter,
precipitable only by half-saturation, the name "<u>pseudo-
globulin</u>." The euglobulin had the power of coagulating
milk, while the pseudo-globulin had a more or less pro-
nounced 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 anti-
body carriers proclaim a real duality and render it high-
ly essential that this mode of division should be retained.

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

Ledingham,[22] 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 percent-
age 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 sus-
ceptible animals.   Different horses display different
reactions to diphtheria toxin.

he states also that the protein ratio in the goat may vary.
Schmidt & Schmidt (1917)[24]   state that the protein ratio
varies considerably in different rabbits and to a somewhat
lesser extent in individual rabbits.

Meyer, Hurwitz & Tanseig (1918)[25]   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 relation-
ship 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-SERUM,
   AND TO OTHER PROTEINS.

According to the theory of Vaughan (1907)[26] and later of
Biedl & Kraus (1911),[27] Freidberger (1913),[28] Pfeiffer (1913),[29]
Schittenhelm & Weichardt (1912)[30] and others the production
of the anaphylactic poisons depends on a splitting of pro-
tein.'

Auer & Van Slyke (1913)[31] have found the cleavage products
of proteins in the blood of animals at the moment of the
anaphylactic reaction.

Doerr & Russ (1909),[32] working with guinea-pigs and using
separated proteins of horse-serum, found that the euglobu-
lin 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)[33] 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 pro-
duced 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 desensitisa-
tion 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 desensitisa-
tion. 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 consider-
able 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 sensi-
tiveness 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),[34] 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)[35] 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)[36] 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.'

D.   THE PRESENCE OF PRECIPITINS IN THE BLOOD.

In regard to the question of the presence of precipitins
in the blood of persons suffering from "serum disease",
Hunter (1905)[37] 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)[38] 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 pati-
ent'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 precipit-
in 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)[39], it also disappears
instantly with anaphylactic shock.

Experimentally, Bulger (1916)[40] 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 antifer-
ment 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 precipit-
ate, larger or smaller quantities causing less digestion.
Kritchewsky (1918) [41] 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 indistinguish-
able 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 pro-
teins 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 preponderence of one over the
others.

Anaphylaxis depends on the introduction into the body of a
foreign protein and on the production of a poisonous sub-
stance 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 sensitis-
ation and desensitisation and also in the length of time
required for the production of the reactions. The anaphy-
lactic reactions are in some cases specific and the specif-
icity 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.

P A R T   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 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) [42]

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-thera-

peutic 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 in-
conceivably 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 anaphy-
lactising 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 mani-
festation 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 anaphy-

lactic 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 varities 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 anti-
toxic principle of the serum. In the anaphylactic reactions
in animals, euglobulin showed more clearly specific sensi-
tiveness 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 substantiat-
ed by experiment and, although the correlation, as suggest-
ed, 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 phenom-
ena 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, pseudo-
globulin 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 pres-
    ent 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 right-
    ing this balance, the blood acts upon the excess of
    protein in the way already described, with the result-
    ing 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 appear-
    ance 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 fre-
    quency 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 been 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 inject-
ions 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 pro-
duction 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 investi-
gation, 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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