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CLINICAL OBSERVATIONS ON SERUM DISEASE

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by

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CLINICAL OBSERVATIONS ON SERUM DISEASE.

It was not long after the introduction of anti-diphtheritic serum as a therapeutic agent that observers realised that in a considerable percentage of cases various untoward phenomena accompanied its use.

It appears that Lublinski was the first to publish in 1894 the records of a case of a girl aged eight years, to whom he had given three injections of 10 c.c. of serum. Nine days after the last injection the child suffered from high fever, swelling of joints, and an extensive macular exanthem appeared.

Since that date various German, French and American writers have published records of cases. Scholz, in 1894: Hartung in 1896: Sevestre & Martin in 1897: while Pirquet & Schick in 1905 published their study on Die Serumkrankheit. English authors have, until comparatively recently, treated the subject with slight attention, but Rolleston has published various papers in the Medical Journals in which he works out a very definite and distinct train of symptoms following upon anti-diphtheritic serum.

I have been able, during six months as Resident Physician in the City Hospital, to watch the effects of anti-diphtheritic serum on 318 cases. I have used anti-streptococcic serum in the treatment of erysipelas and have also, under Dr Ker's supervision, treated by means of intraspinal injections of anti-meningococcic serum, cases of cerebro-spinal meningitis. I have seen manifestations of Serum Disease follow upon the use of all three Serums.

ETIOLOGY OF SERUM DISEASE .

Anti-diphtheria serum has three elements in its composition. First, a small amount of a mild antiseptic as a preservative. Second, the anti-toxic principle. Third, horse serum.

(1) It is extremely unlikely, and has indeed been proved impossible, by experiment, that the injection of so small an amount of antiseptic into the body could produce such large general effects.

(2) The anti-toxic principle: Dr Morley Mathieson, in his thesis on the "Skin in Diphtheria" considers whether the blame for the common anti-toxic phenomena is not to be laid in part to the

charge of a superfluity of the anti-toxic principle. He states that "bacteriological investigation has proved that where too much antitoxin is given, more than is required to neutralise the toxin present, the free antitoxin takes on the action of a toxic substance, and indeed the organism makes provision for defending itself against the new poison by the formation of a new anti-body - an anti-antitoxin." He supposes that this superfluous antitoxin is capable of producing harmful effects because of three facts:

First: Rashes are frequent and severe after an overdose of serum.

Second: Rashes are relatively frequent and severe in cases where little or no diphtheria is present, or after prophylactic doses.

Third: Rashes are very infrequent in severe toxic cases, although large quantities of antitoxin are given."

I find that none of these facts are established by my series of cases. In two cases in my series, I can definitely state that the children had received an overdose of serum. In one case, by my mistake, a child which should only have had 3000 units received 6000 units. In the other case,

due to a coincidence in names, a child in one ward received 4000 units which were meant for another patient, but no symptoms of serum disease manifested themselves in either of these cases.

I have had also to give prophylactic injections of serum to children in a scarlet fever ward in which a case of diphtheria developed, and none of these cases had any serum reaction.

It is also the custom in the City Hospital, to give antitoxin to all cases notified as diphtheria, without waiting for the bacteriological report. I have not found that serum disease was more common among those cases which the bacteriological report declared as negative.

In regard to Dr Mathieson's last fact, that rashes are infrequent in severe toxic cases after large quantities of antitoxin, I find that the most severe case of diphtheria which I have seen and which required no less than 50,000 units of antitoxin developed a beautiful urticarial eruption on the seventh day following her last injection, and certainly she was not overdosed.

I am brought, therefore, by the results of my series of cases, to the conclusion that the antitoxic principle present in serum has nothing to do with the development of serum disease.

(3) Horse serum: It has been proved by experiment that normal horse serum is capable of producing various harmful effects on injection into man. It is now recognised that not only does the serum of one species of animal differ in composition from the serum of another species, but that there may be also differences in the blood serum in animals of the same species. It has been found that the serum of some horses is capable of producing toxic effects in man to a greater degree than the serum of other horses. Certain writers consider that serum rashes were directly connected with precipitin formation in the capillaries. Von Pirquet & Schick, however, showed that rashes often developed before precipitins could be demonstrated, and also, on the other hand, that precipitins may be abundant and yet no serum rashes occur.

It is now held that serum sickness is due to a "chemical reaction between the horse serum and certain anti-bodies in the person injected."

The fact that the horse has been immunised with a certain toxin does not seem to have anything to do with the production of serum sickness.

It is, however, quite possible that an idiosyncrasy on the part of the person injected may be responsible in some cases for some of the ill-effects

produced. That the serum is the responsible agent there can be no doubt when we consider that the reaction to serum was very much more marked in the pioneer days of its use. Since the purification and more careful preparation of the serum, the harmful results are not nearly so evident as they were.

The amount of serum used in an injection appears also to have some bearing upon the production of serum disease.

It seems to be possible that by preparing serums of increasing antitoxin strength, smaller doses will be required to produce the desired effects, and the harmful results which follow injections of a large amount of serum will therefore be obviated.

In New York at present an antitoxic globulin solution, prepared by Dr R. B. Gibson, is being used, and so far the results justify the belief that the rashes and constitutional disturbances which follow the whole serum do not in nearly so marked a manner follow the injection of the globulin solution.

A. SERUM DISEASE FOLLOWING THE USE OF
ANTI-DIPHTHERIA SERUM.

A brief summary of Dr Rolleston's work on this subject may not be considered out of place here, as I find that the record of my cases do not establish his conclusions.

He divides the symptoms of the disease into (a) the early and (b) the late. "Severe pain may be felt at the seat of injection: drowsiness: activity of the sweat glands: local or generalised erythema and diminution of the urinary secretion may be regarded as the earliest symptoms of the disease. There is now a latent period from one to seven or eight days, during which no fresh phenomena are obvious. The second stage is characterised by the development of urticaria. The temperature is seldom raised. Albuminuria may occur simultaneously with the eruption, or pre-existent albuminuria may be increased. The total amount of urine passed in twenty-four hours may also be somewhat reduced. The duration of urticaria is usually about three or four days, but is often much longer or much shorter. Urticaria is the most common of the skin eruptions following the injections of the antitoxin.

"The third stage of the serum disease is not
"always realised, usually separated by one or more
"days from the second. It may become continuous
"with it. The most striking feature of the third
"stage is the development of a rash, at first usual-
"ly an amorphous erythema, but sometimes circinate,
"and almost always becoming circinate subsequently.
"The temperature is usually raised. Malaise and
"anorexia are present, especially in older patients
"who are more likely than younger ones to suffer from
"pains in the joints and muscles. The submaxillary
"and cervical glands and to a less extent the axil-
"lary and inguinal glands become swollen and painful.
"Usually there are no phenomena within the throat to
"account for this neck swelling, but occasionally
"specks may appear on the tonsils or even a continu-
"ous deposit."

Dr Rolleston, therefore, paints a very defin-
ite clinical picture, but although I have carefully
observed the effect of serum in 318 cases, I find
that my cases do not present at all the same clini-
cal picture.

(1) Pain at the seat of injection:

I have found that if the injection of serum is
really subcutaneous, and not into the layers of the

skin, no pain whatever follows on the injection. The site for injection chosen was in the back, just below the angle of the scapula. In several cases in which my injection was not deep enough, the patient has complained of pain and tenderness over the site of the injection.

(2) Drowsiness:

I have given antitoxin in most of my cases at 7 p.m. in the evening. I have, therefore, perhaps, not been able to watch the sedative effect so well as if I had given my injections through the day, but I have certainly found that those cases which I have injected in the daytime were not drowsy after the injection. I have also found amongst my adult cases that their sleep during their first night in hospital was very often broken, and that the serum was not sufficiently a sedative to combat the strangeness of their new surroundings.

(3) Hyperdriosis:

I have seen no case of hyperdriosis following upon injection of this serum. The skin of most patients is certainly moist, but I consider that the fact that most of these cases have a temperature due to their disease, and that we endeavour to keep

patients, by means of blankets and bottles, as warm as possible, is quite sufficient to account for the moist condition of the skin. No patient has ever complained to me of sweating, and I hold that if there was any real appreciable increase in the activity of the sweat glands following the use of antitoxin in any considerable percentage of cases, we would have a history of sweating from patient or nurse.

(4) Diminution of Urine:

There are several factors to be borne in mind in considering this question. Our diphtheria patients are very often children, and in that case it is recognised that it is impossible in most cases to estimate accurately the amount of urine passed. Again, patients on the morning following admission usually get a simple enema, and very possibly some urine is lost, due to that occurrence.

Then we also have to remember that these patients have usually sore throats and are not inclined to drink as much as they would if perfectly well. Indeed, it is often found difficult to get children to swallow as much fluid as we would like them to do.

In eighty-five cases in which I have reason to believe that I have an accurate record of the amount of urine passed, I find that fifty show diminution, for the first few days after admission, as compared with the amount passed during their later time in hospital. In thirty-five patients I find no diminution in the amount of urine passed.

I have not found that there is a diminution in urine during the time when the rash due to the serum is present.

Effect on Temperature:

The literature on this subject would lead one to the conclusion that in a fair proportion of cases the injection of anti-diphtheritic serum produces a rise in temperature.

Northrup, for example, states that "if careful observation be made it will be found that in a good proportion of cases there is a rise in temperature of one or two degrees, coming on four or five hours after injection: this phenomenon is transient, lasts a few hours, and is not generally seen on the ordinary chart, when the temperature is recorded but twice daily."

In the new volume on "The Bacteriology of Diphtheria" practically the same statement is made.

"If careful observations are made, a rise in temperature of one or two degrees, coming on four or five hours after injection, is noticed in a good proportion of cases. This phenomenon is transient, lasting only a few hours and generally escapes observation when the temperature is recorded twice daily in the ordinary routine manner."

Sevestre & Martin quote Lepine, Gordon Morrill and Variot in support of the fact that a rise of temperature does occur in some cases, but admit that it is a variable occurrence and is often inappreciable.

Roux, quoted by the same authority, states that a fall of temperature is to be expected after the injection, in the course of one or two days, but is preceded in a certain number of cases by a rise in temperature a few hours after injection.

It is important to remember in estimating the results on the temperature, the time at which the injection is given. It is obvious that if you give the injection at the time at which the temperature due to the diphtheria is rising, you may in a few hours note a higher reading on the chart which you will be inclined to put down as due to the serum, but which is in reality uninfluenced by the serum at all. In the same way, also, you may happen

to give your injection when the temperature is falling and you may attribute a continued fall in temperature to your injection, which, in reality, is not due to the serum at all. The temperature in diphtheria tends to rise in the evening, although this is by no means a constant factor, many cases showing their highest readings in the early hours of the morning.

I have endeavoured to ascertain accurately in 137 cases the effect of serum injection on their temperature. Most of my injections were given in the evening when the temperature, if it was not inclined to rise, was likely to remain constant for a few hours. The temperature was taken shortly before injection and then hourly for four hours after the injection. The case was then put upon a four-hourly chart.

I counted as a rise in temperature any case where the temperature rose, however slightly, in the hours following the injection. I think that possibly in some cases this small rise in temperature could not be due to the serum but might be due to the patient becoming heated up in bed, the excitement due to their new surroundings, or some other external factor. I consider, therefore, that my percentage of cases in which the temperature

rises should actually be smaller than it is.

In my third list of cases I put charts in which there has been no effect on temperature following the injection of serum.

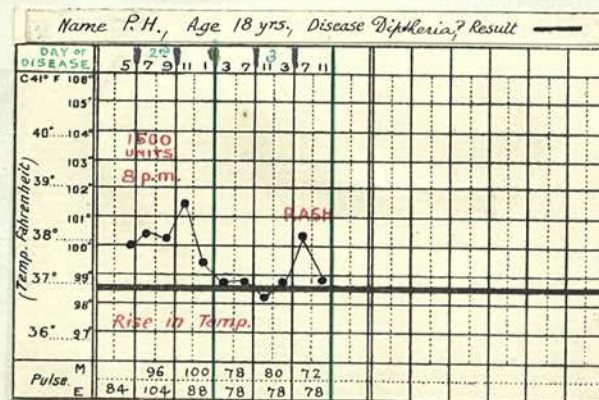
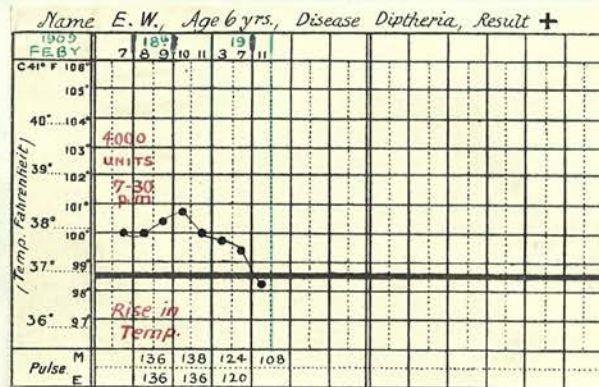
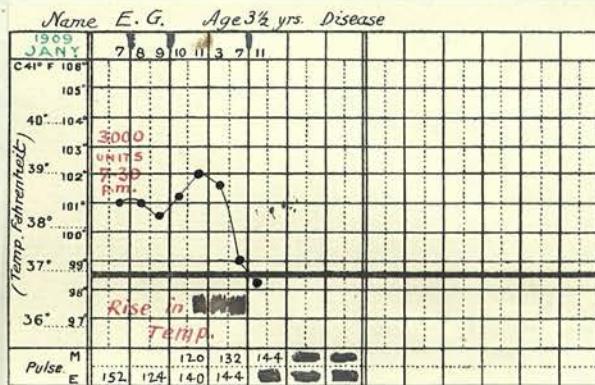
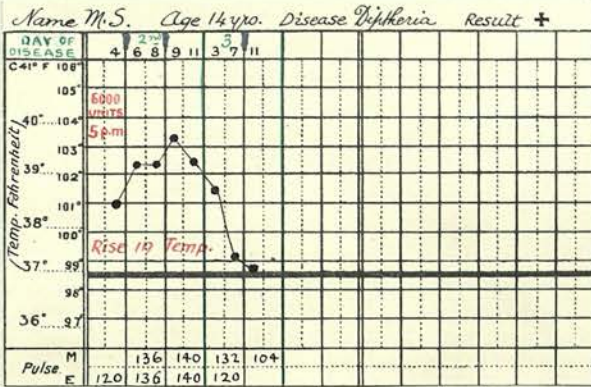
This percentage may be somewhat higher than it should be because I have included in it cases in which there has been a drop of a point or two in temperature, but which have, in the course of the four hours, resumed the level of temperature which they had previous to the injection.

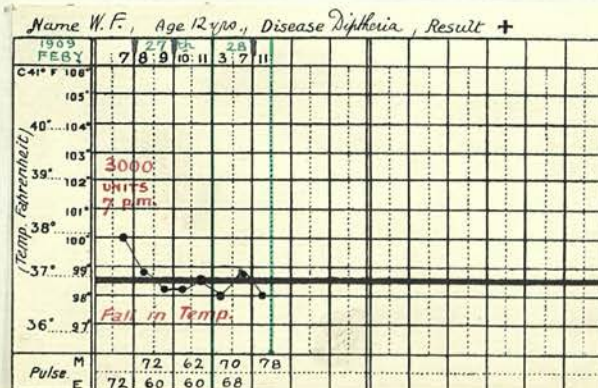
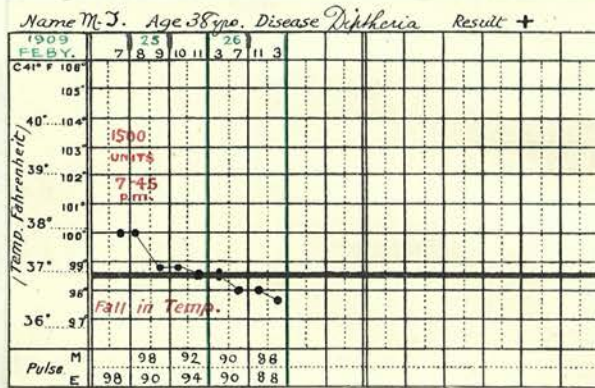
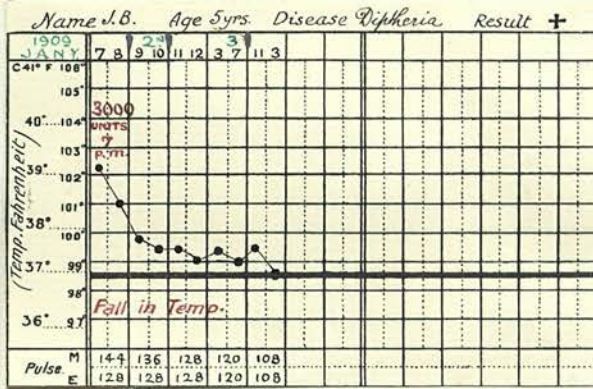
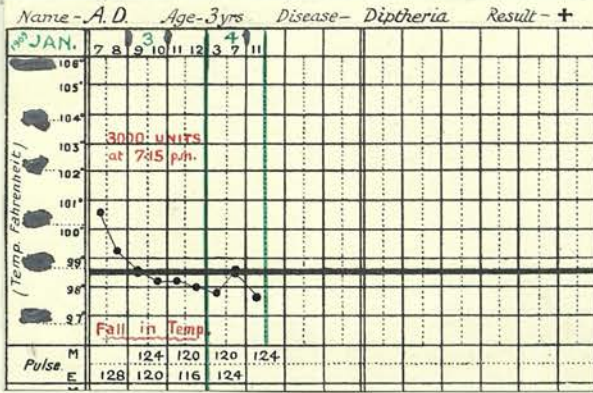
The percentage of cases in which there has been an actual fall in temperature include only these cases in which there has been an undoubted fall and in which the temperature does not return in the course of a few hours to the level previous to the injection.

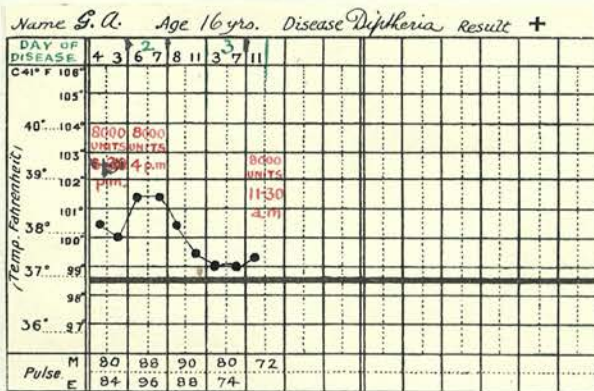
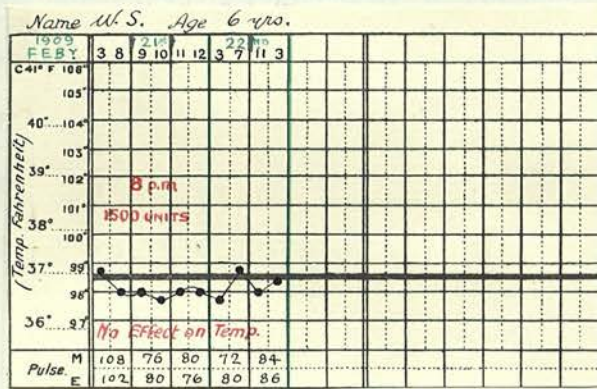
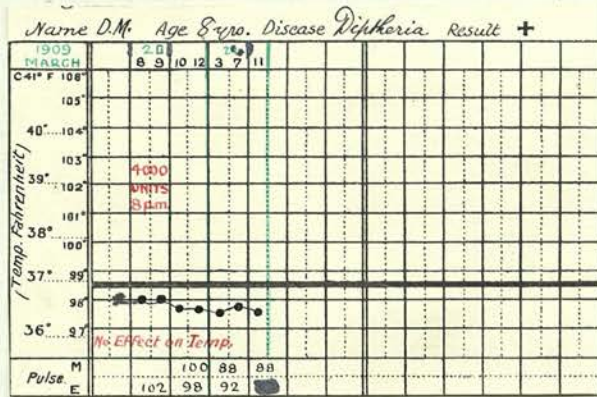
I get the following results in the 137 cases.

31.04% show no effect following the injection.

In 21.9% there has been a rise in temperature, while in 43.06% there has been a definite and appreciable fall of temperature, due, in my opinion, to the injection of the anti-diphtheritic serum, and taken at a time when the temperature chart should not show a falling temperature. I append a selection of charts showing examples of my results.







Effect on Pulse:

I find in many cases that the injection of serum accelerates the pulse. This is more marked in cases in which a large bulk of serum is given. I have not seen a case in which the pulse has become irregular or weaker after injection, and when one considers the undoubted effect of the diphtheria itself, it must be exceedingly difficult to state as to whether a pulse previously quite regular, has become irregular, due to an injection of serum, or is not only being influenced by the disease from which the patient is suffering.

RASHES.

The occurrence of rashes following the injection of serum is by far the most common evidence of serum disease.

Etiology:

The causation of these rashes is by most writers acknowledged to be due to the serum.

Sevestre & Martin put forward an interesting theory for what they term "the exanthemata tardis", meaning the late secondary rashes, which usually occur from the thirteenth to the fifteenth day.

They regard them as possibly due to a streptococcus infection. This hypothesis is based on the character of the symptoms as it is with these late rashes that joint pains and constitutional disturbances occur, and also on the fact that they have found these phenomena in mixed diphtheria or true streptococcic angina and not in pure diphtheria.

Roger, as quoted by Northdrup, while not accepting these conclusions, admits that the serum may have an effect in reducing the resistance of the system to certain organisms comparable to the effect of mercury in mercurial stomatitis, where bacteria are responsible for the secondary phenomena seen in the mouth.

Frequency:

I. The Metropolitan Asylum Board give the following figures:

1898	45%
1899	34%
1900	43%
1901	43%
1902	47%
1903	45%

II. The Edinburgh City Hospital Report gives the following figures for the last three years:

1905	22%
1906	15%
1907	13%

III. The Clinical Society of London report the occurrence of rashes in 35% of their cases.

IV. Hartung quotes European observers as finding rashes in 11.4% in 2661 cases of Diphtheria treated with antitoxin.

V. Berg: In 337 cases which he studied in the Willard Parker Hospital in New York got a percentage of 24.

VI. Roux, as quoted by Sevestre & Martin, reports 14%.

VII. Park, in a paper in the British Medical Journal, reports 3%.

VIII. Rolleston reports extremely high percentages in various series of cases, 81.9% being his highest figure, 69.4 being his lowest percentage.

IX. In my own series of 318 cases, 76 had rashes or 23.8%. Amongst those 76 cases, 10 or 13.1% had secondary rashes.

Reasons for Variation in Frequency:

I. Some authorities have doubtless included amongst their cases very slight and evanescent rashes. It is important also to recognise that many rashes are so evanescent and fleeting that they may be quite easily missed unless very close observation is made.

II. The use of different Sera: It is a matter of common experience that the serum made by certain firms is much more liable to produce rashes than that of others. Indeed, I have found that there is a striking difference in the effects of the serum produced by the same firm.

Some weeks would sometimes pass with no rashes resulting, and then upon the use of certain bottles of serum rashes would appear all through the ward.

It has been my experience also that for a time the rashes would be of a certain variety, then suddenly the variety of rash would change. The time of the occurrence of rashes I found was also inclined to follow the same rule. For some weeks the cases would develop rashes very early in their disease, while at other times all the cases which developed rashes would have them during their convalescence.

Varieties of the Rashes:

There are numerous varieties of rashes described - Erythema, simple or multiforme: Circinate erythema: Scarlatiniform erythema: Papular or Morbilliform eruptions: and Urticaria.

I have classified these 86 rashes as follows:

Morbilliform	28 or	32.5%
Urticaria	27 "	31.3%
Erythema Multiforme	16 "	16.2%
Erythema scarlatiniform	11 "	12.7%
Erythema simple	3 "	3.6%
Erythema circinate	1 "	1.1%

It is interesting to note how the relative frequency changes. Dr Morley Mathieson, in his series of fifty-three cases from the same Hospital records,

Urticaria	38.
Erythema, simple or blotchy	6.
Erythema, scarlatiniform	4.
Morbilliform	2.
Erythema circinate	0.
Mixed	3.
Petechial	0.

Stanley reports from observations on cases in the Hospitals of the Metropolitan Asylum Board circinate erythema as the most common antitoxin rash.

Rolleston, working at a later date in the same Hospitals, reports urticaria as by far the most frequent eruption.

Time of Occurrence:

I. The Investigating Committee of the Clinical Society of London produce the following figures out of 633 cases:

33	had	a	rash	between	the	1st	and	6th	days.
147	"	"	"	"	"	7th	"	12th	"
34	"	"	"	"	"	13th	"	18th	"
6	"	"	"	"	"	19th	"	31st	"

II. An analysis of The Reports of the Edinburgh City Hospital for three years has given me the following figures. Out of 242 cases,

75	had	a	rash	between	the	1st	and	6th	days.
116	"	"	"	"	"	7th	"	12th	"
45	"	"	"	"	"	13th	"	18th	"
6	"	"	"	"	"	19th	"	31st	"

III. My own series of 86 rashes gives me the following results:

54	had a rash between the	1st	and	6th	days.
24	" " " " "	7th	"	12th	"
8	" " " " "	13th	"	18th	"
0	" " " " "	19th	"	31st	"

As regards the variety of rash and its time of occurrence.

Morbilliform rashes: 25 between the 1st and 6th days

1	"	"	7th	"	12th	"
<u>2</u>	"	"	13th	"	18th	"

Total 28
==

Urticarial Rashes: 10 between the 1st and 6th days

15	"	"	7th	"	12th	"
<u>2</u>	"	"	13th	"	18th	"

Total 27
==

Erythema Multiforme: 8 between the 1st and 6th days

5	"	"	7th	"	12th	"
<u>3</u>	"	"	12th	"	19th	"

Total 16
==

Erythema Scarlatiniform: 8 between the 1st and 6th days

1	"	"	7th	"	12th	"
<u>2</u>	"	"	13th	"	18th	"

Total 11
==

Erythema Simple: Total 3 between the 1st and 6th days.

Erythema Circinate: Total 1 on the seventh day.

These figures shew that the cases which have had morbilliform rashes have had these rashes at an earlier time than is usually recognised.

The cases which have developed urticaria have spread themselves almost equally over the first twelve days after injection.

Secondary Rashes:

In my ten cases of Secondary Rashes, I find that the second rash was in three cases urticarial in type: in four cases morbilliform: in two the rash was multiforme erythema, while one case developed a beautiful scarlatiniform eruption.

Rashes Considered in Detail.

Morbilliform Eruptions:

Out of the twenty-eight cases, twenty-five of these rashes were within the first six days after the injection of serum. Two of these rashes were secondary to a previous eruption of another character.

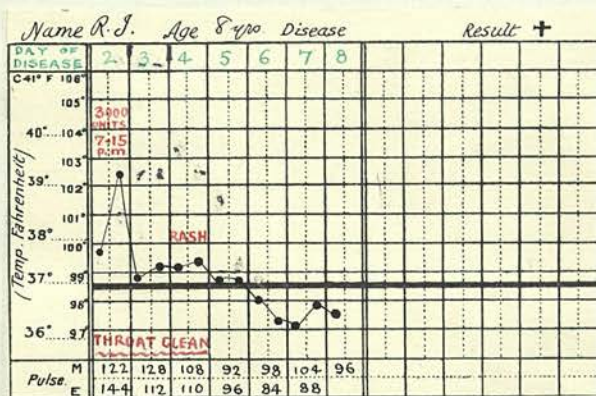
I consider a morbilliform eruption to be an eruption of a pinkish colour, and raised maculopapular in character. The distribution of an eruption of this kind has not kept me from including it amongst morbilliform rashes, although unlike measles or German measles, the antitoxin rashes have often spared the face.

Illustrative Cases:

Case I.: P.I., aet 8, female.

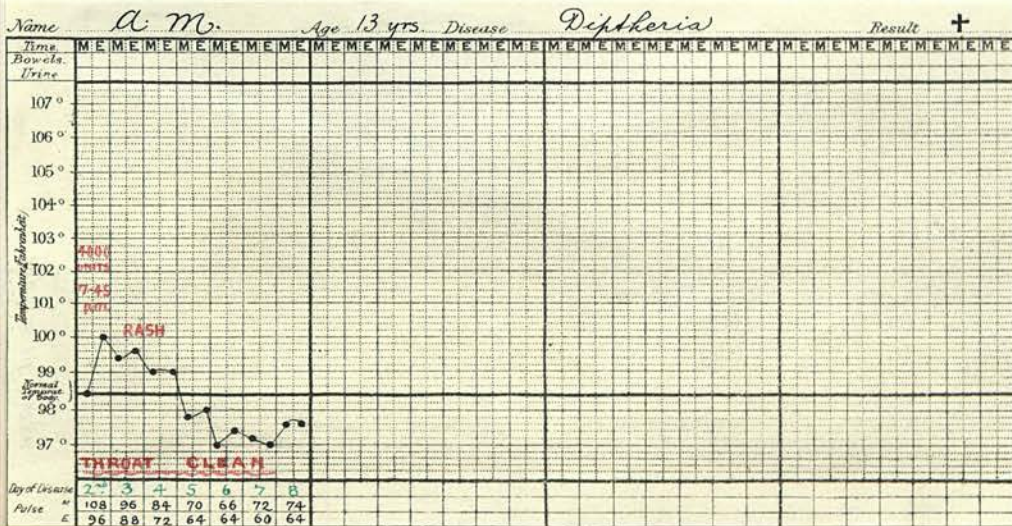
Was admitted on the second day of her disease. She was suffering from faucial diphtheria and the swab taken from the throat gave a positive result. She received 3000 units on the evening of admission. Her throat cleaned up within two days. On the second day after admission, a rash appeared on arms and legs. This rash was morbilliform in colour and raised papular in character. Later in the day the rash appeared on the trunk and face. A photograph was taken of the legs, which I reproduce below. In the evening, the rash on the legs had run together and become blotchy, the rash on the body still remaining discreet. On the following morning it was faded altogether. There was no constitutional disturbance, no rise in temperature, no albumin, the diazo reaction was negative, and the

child developed no other symptom later of serum disease.



Case II. A.M., aet 13, male.

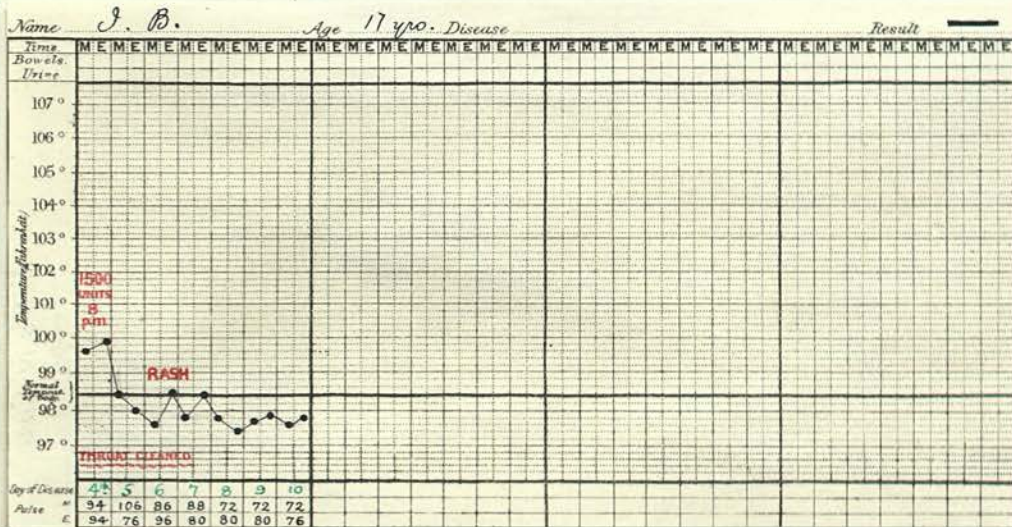
This patient was also admitted on the second day of his disease, with a history of sore throat, headache and shivering. The left tonsil was enlarged and was covered with a grayish-white patch of membrane. The right tonsil had a small speck of membrane upon it. The glands in the left side were enlarged. The swab taken resulted in a positive report. He received 4000 units at 7-45 on the evening of admission. On the following afternoon a raised papular eruption appeared, commencing round seat of injection, and spreading on to face, arms, trunk and limbs. The rash was blotchy over the buttocks. On the morning following, the rash was still bright upon the patient, but the colour had changed. It was distinctly bluish. His eyelids were puffy and his conjunctivæ were reddened. He complained of slight itching. The rash had entirely disappeared on the next morning, and patient made an uneventful recovery.



Case III. I.B., aet 17, female.

Patient was a servant girl and was admitted along with two other cases of diphtheria from the same house. She was on the fourth day of her disease. She had had measles three years before. The throat was slightly congested with small specks of white material upon both tonsils. The swab report was negative. She got 1500 units of antitoxin at 8 p.m.

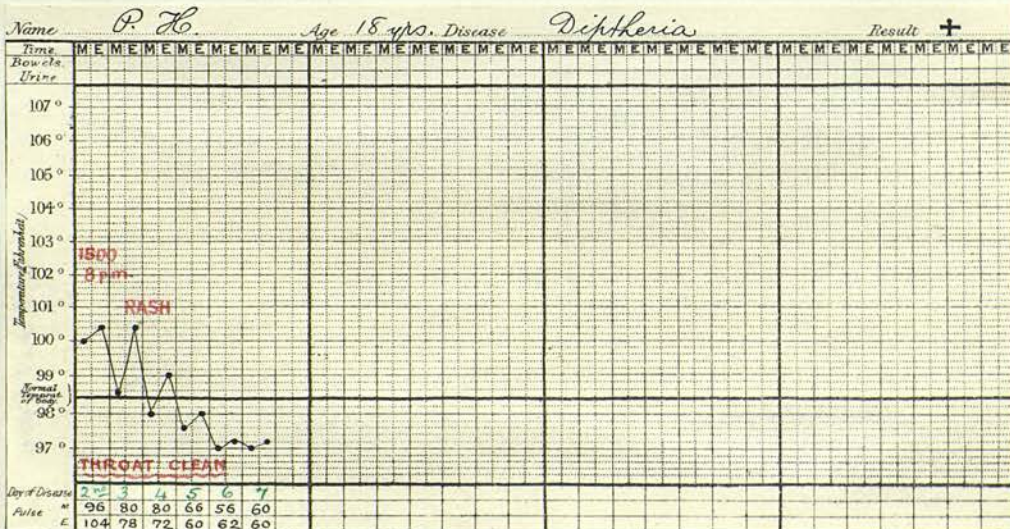
Two days after admission a well-marked papular erythema appeared round the seat of injection, and spreading upwards over the shoulder. By the evening a beautiful raised red scattered papular rash was all over patient's body. This rash was slightly itchy and had run together round the knee-joints. By the following morning it had entirely disappeared. Her four-hourly chart showed a well-marked fall after the injection of serum.



The following case is a good example of a rise in temperature after antitoxin and of a morbilliform rash appearing early, while it shows also a rise of temperature with the coming out of the rash.

Case IV. P.H., aet 18, male.

Came to Hospital on the second day of his disease with a positive throat. He received 1500 units at 9 p.m. On the evening following a papular erythema came out all over the body. His eyes were somewhat swollen, but he complained of no itchiness or discomfort. The rash was entirely faded in twenty-four hours, and patient had no other symptom of serum disease.



I will now give the notes of two cases in which the morbilliform rash came out later and which were also complicated by joint pains.

Case I. J.C., aet 6, female.

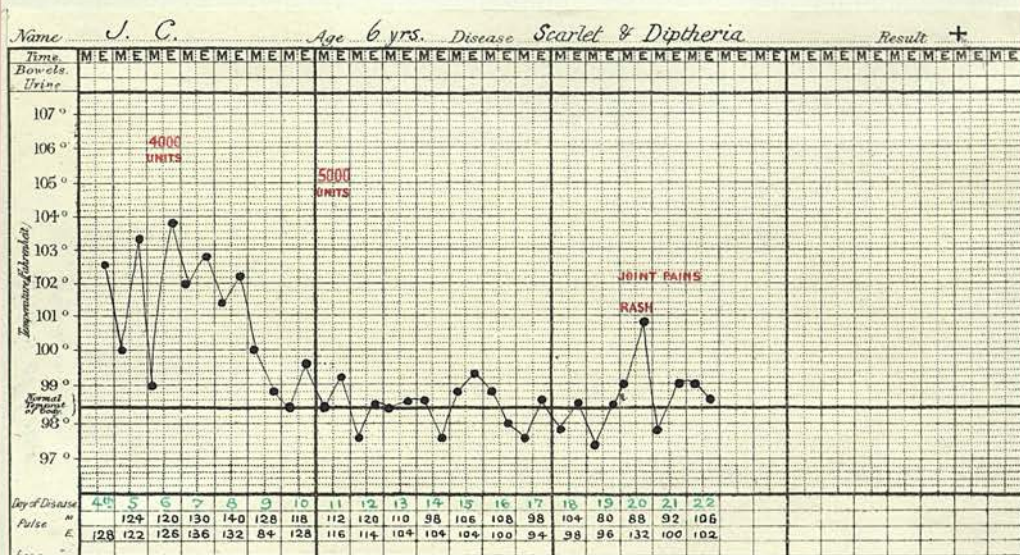
This child was admitted as a case of scarlet fever, with a history of shivering, vomiting and sore throat, four days previously.

She had a typical attack of scarlet fever, but there was also distinct patching on both tonsils. This patching made one suspicious that we were dealing with a case of concurrent scarlet and diphtheria.

The swab taken was positive and she received 4000 units, but this, five days later, had to be followed by another dose of 5000 units, as the membrane on one tonsil appeared to be spreading.

On the fourteenth morning following her first injection the eruption appeared as a macular erythematous rash on arms and legs and was distinctly morbilliform in colour. The rash spread over the trunk and face. On the evening of that day her temperature went up to 101° and she complained of very severe pain in her hip-joints. The joints were swollen and very tender. The child could not be persuaded to attempt to move her limbs but the knee and ankle joints were not affected. The next morning the rash was entirely gone, but the pain in the joints remained for another twenty-four hours. She had no albumin in her urine. On admission the diazo reaction was present in the urine, but the

reaction was negative during the period of her serum sickness.

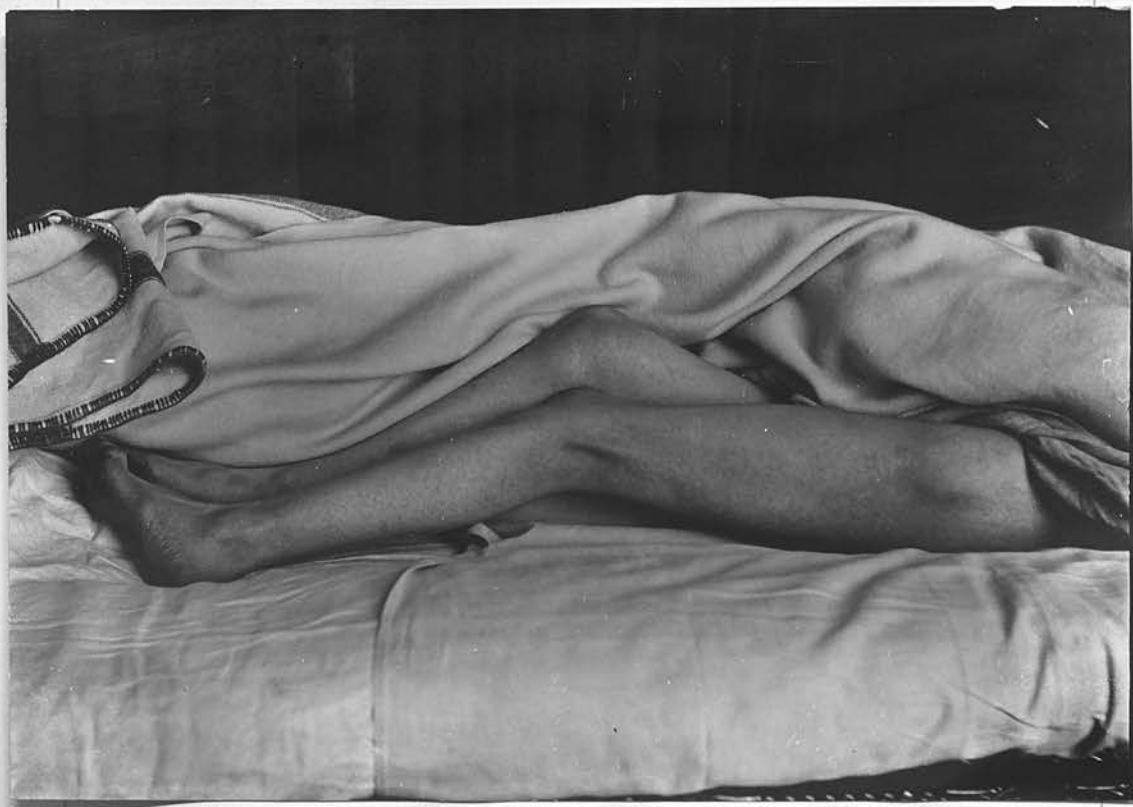


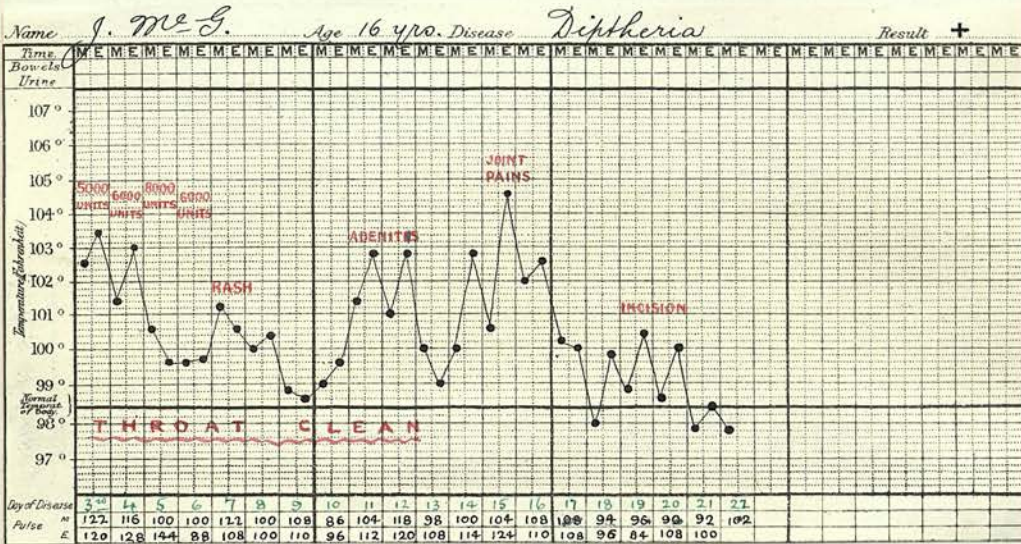
Case II. J.M., aet 16, male.

He was admitted on the third day of his diphtheria and his throat was congested and swollen, with both tonsils well patched with grayish-white membrane. The glands on both sides were definitely enlarged. He received 5000 units his first afternoon in Hospital, 6000 units the second day, 8000 units on his third day, and a final dose of 6000 units on his fourth day, making in all a dose of 25,000 units. The glands, however, had subsided by the fourth morning, but the patient's throat did not finally clean up for about ten days. The first sign of serum disease appeared on the morning of his last injection. A well-marked,

finely scattered, papular erythema appeared all over the body and arms. The face was covered with a blotchy rash. The rash had a characteristic bluish tinge. On the following morning the rash was still faintly present, but not entirely faded by night. His next development was a secondary adenitis of the glands of the neck. They became again very swollen and painful and finally broke down, and an incision had to be made and the pus evacuated eight days later. This is the only case in which I have seen suppuration following upon either the so-called serum adenitis or the late adenitis of diphtheria.

On the evening of the eighth day after the rash had faded, the patient's temperature went up to 104.6° . He complained of pains in the legs, not at first in the joints. On the following morning, however, his ankle, knee and hip-joints were swollen and painful. His metacarpo-phalangeal joints were also affected. Patient could not move easily in bed, and the joints were formented with tincture of Belladonna. The swelling and pain of the joints had entirely disappeared by the evening of the following day. This patient developed no secondary rash. He had albumin in his urine while his rash was present. This albumin returned when the joint pains and swollen glands were present.



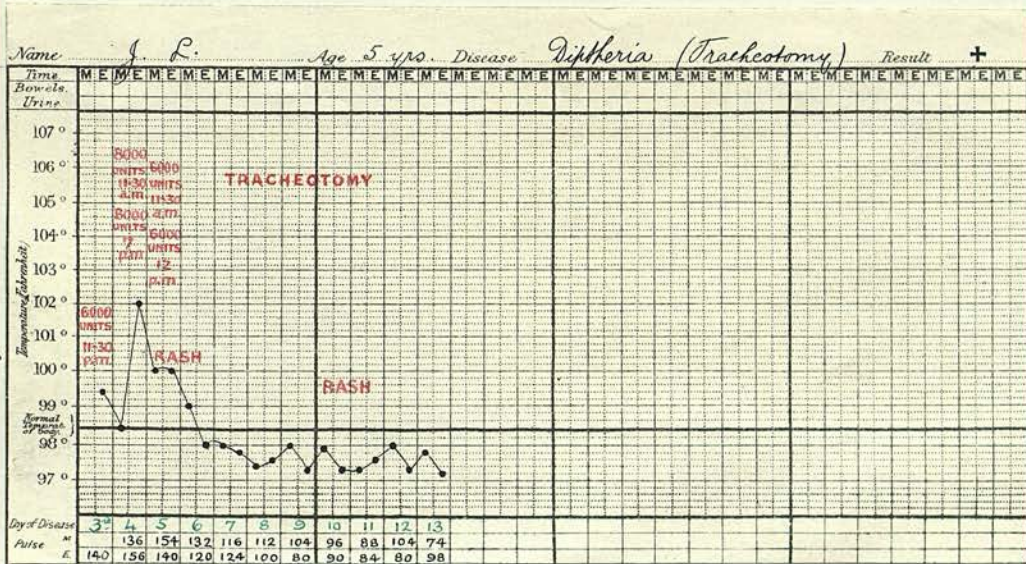


I will now give the notes of two cases to show that morbiliform rashes may appear as either primary or secondary rashes following serum injection.

Case I. J.L., aet 5, male.

This child was admitted with a history of vomiting and croup. He was on the third day of his disease and on admission was suffering from very marked dyspnoea. His tonsils were patched and a swab taken from the throat and examined directly was positive. He was placed in steam and received 6000 units of antitoxin. His condition did not improve and I performed tracheotomy which relieved the condition. On the next day he received 16,000 units in doses of 8000 units, and on the following day 12,000 units in doses of 6000 units, making a total of 34,000 units. On the day following his last in-

jection a bright scarlatiniform rash appeared round the seat of injection and spread all over the body. This rash faded in twenty-four hours. Five days after his last injection a papular rash came out all over legs, arms and trunk. The face was not affected. This rash was extremely itchy although it was not urticarial on any part. It lasted for forty-eight hours and was best marked on the extensor aspect of limbs. Patient had no albumin and no constitutional disturbance. After this rash faded, he made a very satisfactory and complete recovery.



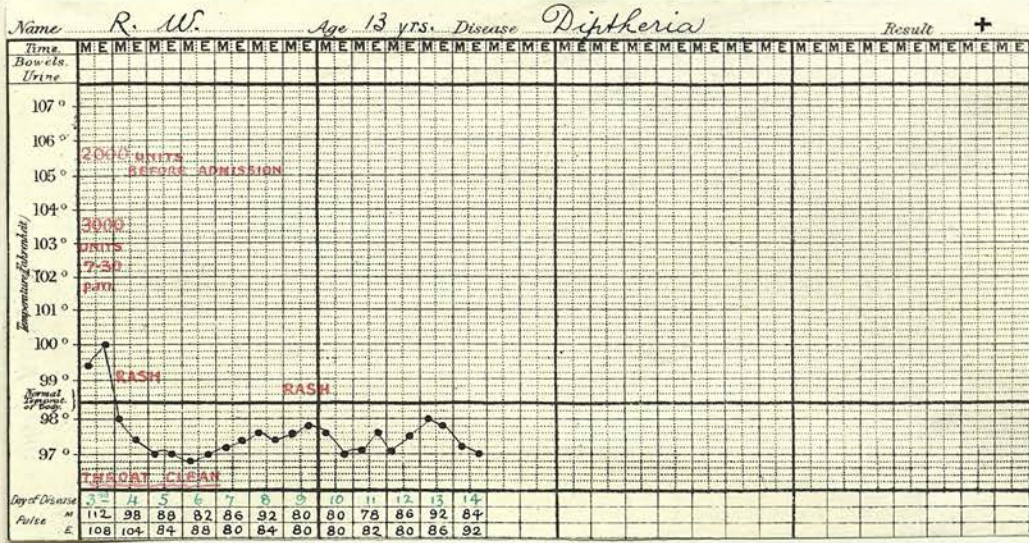
Case II. R.W., aet 13, male.

This boy had 2000 units of antitoxin on the evening before admission, given into the skin of the abdomen.

He had a large patch on one tonsil of thick

membrane and he received 3000 units on the evening of his admission. The throat cleaned up in three days. On the day following his admission the seat of injection in the abdomen was marked out by a large patch of simple erythema, while a finely scattered papular erythema appeared on the legs and trunk. The arms were not affected. This eruption was more intense round the joints, and did not fade for three days. The secondary rash came out six days after the last dose of serum, preceded by itching and redness over both areas of injection. The rash was urticarial in type and was distributed all over the body. It was extremely itchy and went away and returned again several times.





Conclusions:

These specimen cases, then, show that morbilliform eruptions were in my series of cases a common antitoxin phenomenon. They occurred either as the only evidence of serum disease, with or without a rise in temperature, or as part of a more serious disturbance in the cases where the joints were implicated. They also occurred either as the primary rash or as a secondary rash.

Differential Diagnosis:

Measles: The rash itself is the only cause for a mistake in diagnosis between a morbilliform eruption following antitoxin and true measles.

(1) In true measles you would have a previous history of catarrh: you would have also before the

eruption the presence of Koplik's spots on the buccal mucous membrane.

(2) Temperature: In measles the temperature will have reached generally at least 102° before the rash appears. Accompanying an uncomplicated morbilliform eruption you will not find such a high temperature.

(3) Distribution of the rash: In measles the face is always involved but is often avoided in morbilliform antitoxin rashes.

(4) The diazo reaction in the urine is present in over 80% of cases of true measles. It is absent in all cases of antitoxin rashes.

German Measles: There is distinctly more difficulty in diagnosis between German measles and certain morbilliform eruptions. The absence of the diazo reaction does not help one to a diagnosis, this reaction being absent in German measles also.

(1) Character and distribution of the rash: In an antitoxic eruption the rash, although in places it may be distinctly like German measles, will show in other parts distinctive differences, in colour or in character. The face, which is always affected in German measles, is usually spared or affected after the body, in an antitoxic eruption.

The fine distinctive spotting on the dorsum of the feet in German measles will not be present in the antitoxic rash. The antitoxin rash again will tend to concentrate itself round the joints.

(2) Presence of Glands: Enlargement of the glands in the sub-occipital triangle will not be present in an antitoxic rash, although the axillary glands, especially if your injection was made into the back, will often be enlarged in both conditions.

Urticaria:

By an urticarial rash I understand an eruption which takes the form of raised wheals, white in colour and resistant to the touch. The white wheals are surrounded by a reddened area. The eruption varies much in its intensity. It may be very slight with no itching or irritation or constitutional disturbance, or it may cause intense discomfort and also vomiting and sickness may precede or be coincident with the rash.

(1) Locality and distribution: It very often starts at the seat of injection and spreads from there all over the body. It is frequently best marked around joints, and in the folds of skin.

The rash spreads so rapidly and disappears often so quickly that it is difficult in many cases to say where it definitely started.

(2) Evanescent character of the rash: I have found this eruption to be the most evanescent of all antitoxin rashes. It comes out and disappears and then comes out afresh in a very short period of time. I have often found that on uncovering a patient the rash will reappear. It is difficult to estimate how long such an eruption is present. In some cases I have seen it last for several days, in other cases only for a few hours.

(3) Influence of age and sex: There was no evidence of any influence due to the age or sex of the patients.

(4) Temperature: It is sometimes accompanied by a rise of temperature.

(5) Irritation and Itching: This variety of rash is the one which causes most discomfort to the patient. I have had cases of morbilliform rashes causing itching, but practically every case of urticaria complained of discomfort due to the itching.

Treatment:

I have tried a menthol ointment suggested by Rolleston, (Menthol $\mathfrak{3}$ i Par. alb. Moll. $\mathfrak{3}$ i) and

have found it has, in most cases, relieved the irritation. In children it is necessary, however, if you are using this ointment, to restrain the hands in splints, otherwise, as in one of my cases, the child will certainly rub his eyes with his ointment-stained fingers, and the irritation of the urticaria will be forgotten by the new irritation caused by the menthol. I have found in children that sponging with a solution of bi-carbonate of soda is very helpful and allays discomfort.

Illustrative Cases:

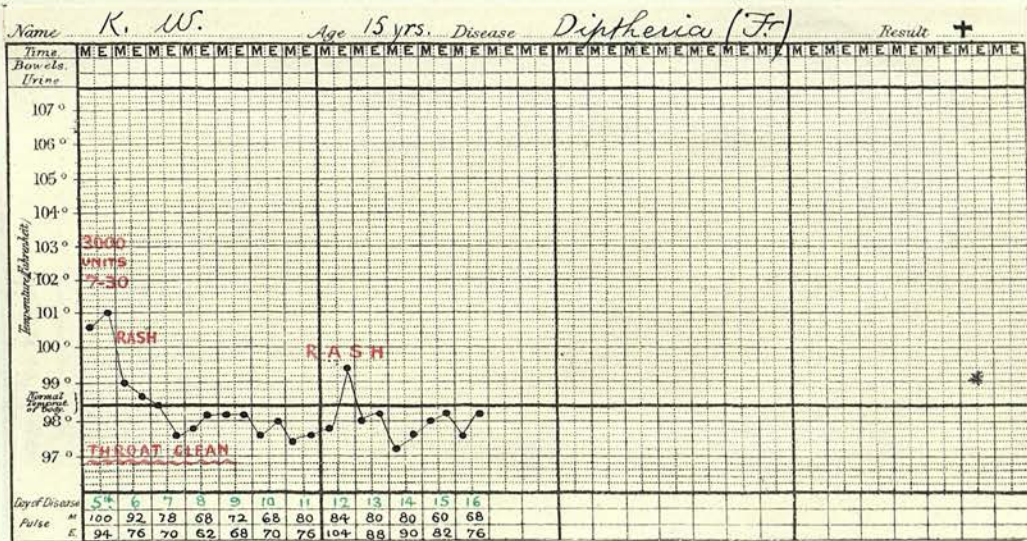
Urticaria, without a rise in temperature.

J.M., aet 5, male.

Was admitted on the third day of his disease with a history of sore throat and croup. On admission he had difficulty with his respiration: there was distinct indrawing on inspiration, but this was relieved by steam. He received 6000 units of anti-toxin.

On the fourth day in hospital he developed an urticarial eruption: the rash came out on his back, and spread upwards over the shoulders and round the neck. It came out later on the arms and legs. The face was not affected. He complained much of the irritation due to the rash, but there was no rise of

five days from the injection and started definitely at the seat of injection. It spread all over the body, coming out and disappearing, and lasted for fully three days. The temperature rose in the evening of the second day of this rash. The boy did not complain of irritation but he had been treated early with menthol ointment.



Erythema multiforme:

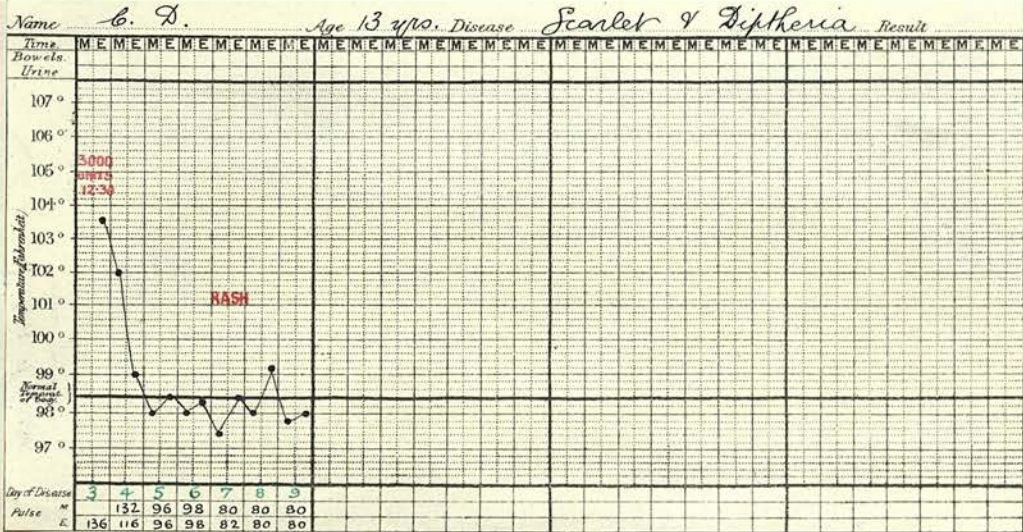
I have classified under this name all mixed erythematous rashes. Any rash which I could not place under the other five heads I have placed among these multiform erythemas. They have occurred at varying times, either early or late after injection. They have also, as already mentioned, occurred as secondary rashes. This variety of rash occurred in sixteen of my 86 cases.

Illustrative cases:

Case I. C.D., aet 13, female.

Was sent in as a case of diphtheria with a history of headache and sore throat. Her tonsils were patched but her tongue was highly suspicious of a third day scarlet fever patient, while the remains of a scarlet rash could be seen on the skin in the bend of the elbows. She received 3000 units of anti-toxin and was isolated in a side ward. Her tongue cleaned up, and by her subsequent desquamation, she proved that she had been a case of scarlet fever.

Four days after her injection a multiform erythematous rash appeared at first round the seat of injection. It spread all over the body and varied in character. In parts it was papular, in other places it simply consisted of raised erythematous patches, while the back and buttocks had a finely punctate scarlatiniform eruption. The rash was entirely gone on the next day, although the temperature went up to 99.2°.

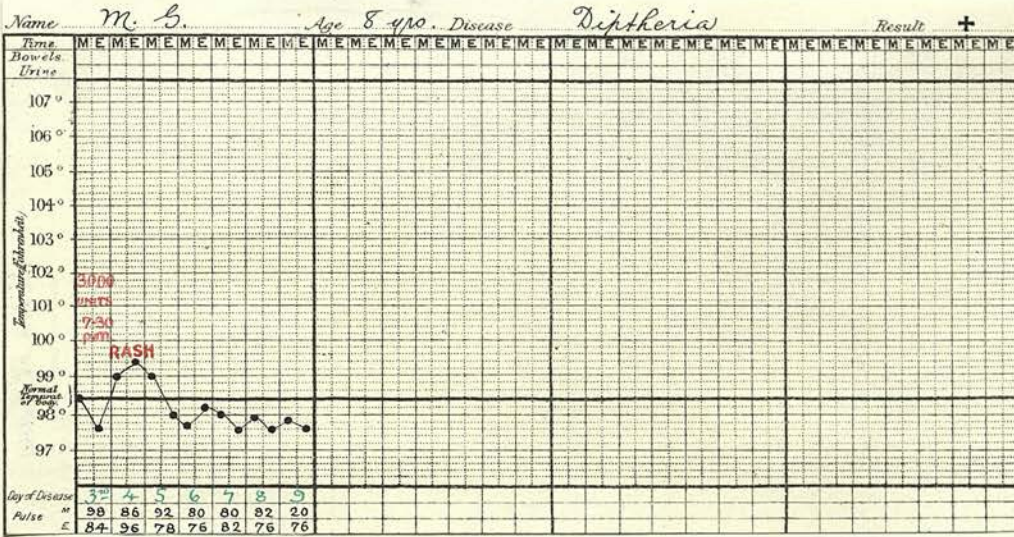


Case II. M.T., aet 10 months, female.

This patient was admitted on the seventh day of her diphtheria with a history of croup. She was breathing very badly on admission and I had to perform tracheotomy at once. The operation relieved the dyspnoea. She had 20,000 units of antitoxin spread over forty-eight hours. On the eighth day after her last injection she developed a multiform erythema which spread all over the body. This rash was beautifully symmetrical round both wrists and ankles. It faded the next day.

Case III. M.G., aet 8, female.

Was admitted on the third day of her disease with a history of headache, sore throat and croupiness. Both tonsils were patched, and she received 3000 units. Only twelve hours after injection a rash appeared. It came out first in the face and then two symmetrical patches of erythema appeared on both wrists. The rash then spread over the trunk and limbs, varying in character. The next evening it was still bright upon the patient but while it was distinctly scarlatiniform on the body, the legs were covered with a papular, scattered erythema. Albumin was found in the urine, and the rash lasted for two days.



Scarlatiniform:

I have had eleven cases of true scarlatiniform rashes in the present series. Scarlatiniform rashes occur so frequently from a variety of causes - hot baths, drugs, enemata, or as prodromal rashes to various eruptive fevers, such as measles or chicken-pox, that it is necessary to carefully eliminate these various other conditions before putting down such an eruption to the antitoxin.

Scarlet fever itself may be so simulated by an antitoxin rash that it is often a very difficult matter indeed to come to a diagnosis between the two conditions, though this is not so important a matter in private practice where a case of diphtheria will be isolated alone, still in Hospital practice a whole

ward may be infected with scarlet fever if a case of true scarlatina be labelled "antitoxin".

Differential Diagnosis:

(1) Previous history of the case: The history may help one to arrive at a diagnosis. If your eruption is preceded by vomiting, rigors, sore throat and headache, you will naturally conclude the patient is suffering from scarlet fever as such a history would be very uncommon as a sequel to antitoxin.

(2) Temperature: A high temperature would be in favour of scarlet fever.

(3) Pulse: Acceleration of the pulse, a pulse more rapid than the height of the temperature demands, would help to a diagnosis of scarlet fever.

(4) The Tongue: Not much dependence can be placed on my opinion on the tongue. You may get positive evidence later when the tongue assumes a typical fifth day strawberry appearance. At the time your diagnosis is in doubt, however, you will often find in a case which will not be scarlet fever, a white furred tongue, with projecting and enlarged papillae.

(5) Rash:

(a) There is a peculiar bluish tinge about an antitoxin rash which it is impossible to describe,

but which, if it is present, one will always recognise. This peculiar colour will sometimes aid one in diagnosis.

The vivid brightness of the true scarlet will be absent in most cases.

(b) Distribution of the rash: If the rash is observed while coming out, much help will be obtained. If it is an antitoxic rash, it will usually appear round the seat of injection and spread from there over the body. The face, though flushed, will not give the definite circum-oral pallor so characteristic of scarlet fever. In its spread also the antitoxin rash is often erratic, missing portions of the skin, while in scarlet fever the rash usually steadily advances from the neck downwards.

(c) Diazo reaction: I have endeavoured to test the value of this reaction as a point for use in differential diagnosis. I have tested the urine of all my cases which have had antitoxin rashes and they all give a negative reaction. I have had tested 100 consecutive cases of scarlet fever and 35% of these give a positive reaction: therefore, a positive diazo reaction would be of a certain value in deciding whether or not a case is scarlet fever, while a negative result would, however, not exclude the disease.

(7) Desquamation: This is too late to be of practical value. It may be also misleading as patients after a severe antitoxic rash will desquamate freely. If you get typical desquamation of the hands you should be able then to classify your case.

Scarlatiniform antitoxin rashes are usually early rashes occurring soon after the injection of the serum. I have one case, however, in which a scarlatiniform rash appeared as a late secondary rash.

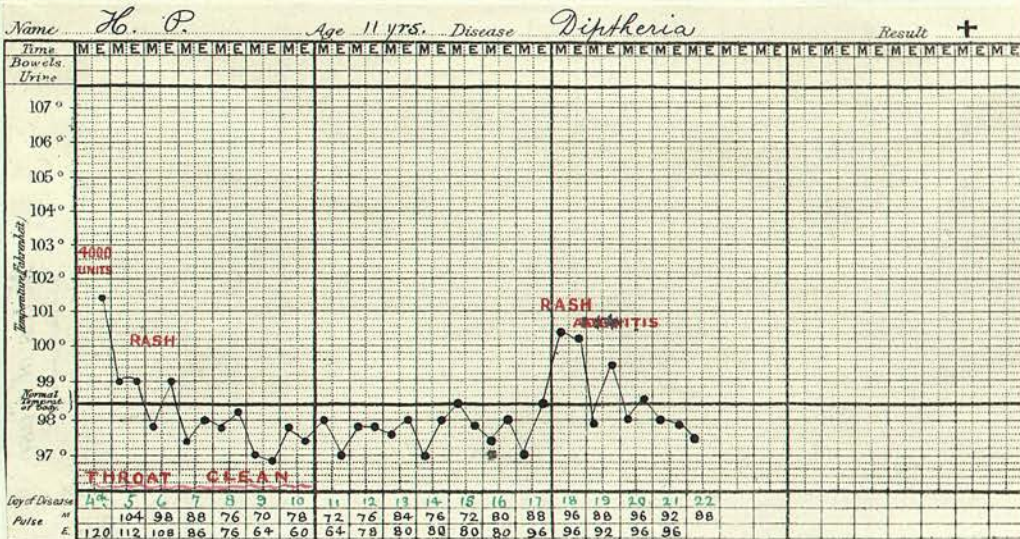
Illustrative Cases:

Case I. H.P., aet 11, male.

Was admitted with faucial diphtheria on the fourth day of his disease. He received 4000 units of antitoxin.

On the next day a multiform erythema appeared all over the body and lasted for two days. Thirteen days after injection another rash came out in the evening. This appeared as a bright scarlatiniform rash. It began at the seat of injection and spread all over body. The boy's face was flushed, his eyelids puffy and his conjunctivae red and congested. The following morning the temperature went up and the rash had almost faded. He complained of pain in his right knee-joint, and he developed secondary adenitis.

The fact that the temperature followed the rash, which was also very fleeting, and that at the same time he had other symptoms of serum disease, made one certain of the diagnosis. The patient remained in the ward, did not desquamate, and made an uneventful recovery.

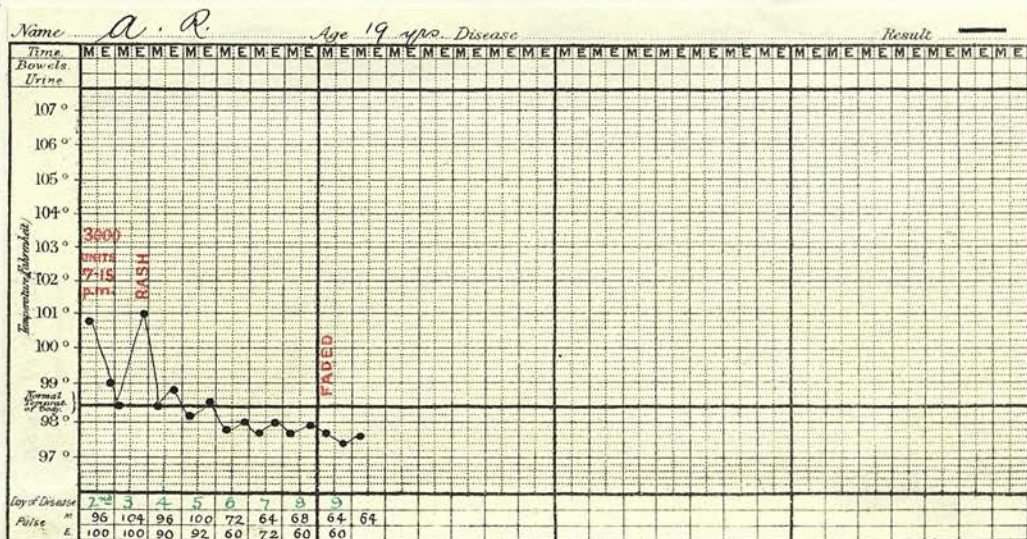


The next case is a case of true scarlet fever, which developed soon after the antitoxin. The case was so difficult from the point of view of the diagnosis that it was not until really typical desquamation occurred that the patient who was isolated in a side ward was sent to a scarlet fever ward where she did not contract scarlet fever.

Case II. A.R., aet 19, female.

Was admitted on the second day of her illness as a case of diphtheria with a history of sore throat and shivering. She received 3000 units of antitoxin. The culture from the throat was negative as regards diphtheria.

On the evening following injection, the temperature went up to 101° and a bright scarlatiniform eruption came out on the body. It appeared more intense round the joints. The tongue was not typical, but the rash remained bright upon the patient for five days. The tongue never really cleaned up. She finally desquamated like a typical scarlet and was removed to a scarlet fever ward where she remained six weeks.



Case III. J.A., aet 20, male.

Admitted with a history of sore throat, headache and shivering. He was on the fifth day of his illness. The throat was patched and the swab taken gave a positive result. He received 4000 units of antitoxin.

He developed three days later with a normal temperature a bright scarlatiniform rash which started round the seat of injection. The face had no rash, but was flushed. There was no circumoral pallor. The rash the next morning was all over the body and a photograph of the back was taken. The legs were well marked but the wrists and ankles were clear. The patient had no constitutional disturbance. The following day the rash had faded but had left haemorrhagic staining.

The patient desquamated, but the desquamation was fine in character, not flaky as in a scarlet. He developed later a secondary angina and his glands became swollen but finally he made a satisfactory recovery.

Case IV. J.G., aet 3, female.

This child was admitted with a patched throat, and a history of sore throat and vomiting. The throat was negative. She received 1500 units of antitoxin and on the following day a bright scarlatiniform eruption appeared on neck, back, arms and legs. The rash came out round the site of injection and spread over the body. Some parts of skin were left unaffected by the eruption which faded the next day.

Simple Erythema:

I have had three cases of simple erythematous rashes. These rashes occurred early, within the first six days after injection, and did not last longer than twenty-four hours.

Circinate Erythema:

I have had only one case of circinate erythema. This occurred as a primary rash and was followed by an urticarial eruption some days later. This case is interesting, as one would imagine, from Rolleston's papers, that circinate erythema is always a secondary eruption, and that urticaria is always the primary rash.

Mrs M., aet 33.

Was admitted with a history of sore throat and shivering. She had had 2000 units of antitoxin on the evening before admission and as the throat was already cleaning up she received no antitoxin in the Hospital.

On the seventh day after her admission a circinate erythema came out on the back: the rash appeared through the night. It spread all over the body, and was specially well marked on the legs. Symmetrical patches appeared round both knee-joints. The rash was entirely faded by the next morning.

This patient developed, 48 hours after the fading of this circinate eruption, an urticarial rash which came out all over the body. The raised wheals of the urticaria were specially prominent on the abdomen. The irritation resulting from this eruption kept the patient from sleep and it was still bright the next morning. The rash had faded by the next day and the patient gave no further evidence of serum sickness. She had a trace of albumin in the urine coincident with the urticaria.

JOINT PAINS.

Pain and swelling of the joints following upon injection of anti-diphtheritic serum appear to have been more frequent in the early anti-toxin days than it is now.

I have analysed the City Hospital Reports for the last three years and find a very small percentage.

	Cases.	Rash & Joint Pains.	Joint Pains alone
1905	488	8 or 1.6%	3
1906	462	9 or 1.8%	2
1907	419	4 or .93%	3

My own figures are as follows:-

No. of Cases.	No. of Rashes.	Rash & Pains	Joint pains alone.
318	76	7	1

That is a percentage of 2.2% out of 318 cases injected with serum while it is a percentage of 9.2% out of the 76 cases which gave evidence of serum disease by various rashes.

Date of Occurrence:

Joint pains are usually a late phenomenon in Serum Sickness. The one case in which I had joint pains without any rash occurred on the sixth day. One other patient complained of pain in his right shoulder six days after the last injection of serum. In the remaining five cases three had joint pains on the tenth day and two on the eleventh day from their last injection.

Joints Affected:

Any joint may be affected by this serum arthritis. The shoulder, hip and knee joint were the joints most affected in these cases. Other observers have placed the metacarpo-phalangeal joints as the joints most frequently involved.

Pain:

This is a marked feature of the condition. A patient often complains of severe pain which is intensified if you attempt to move the affected joint.

Temperature:

Patient has usually a high temperature throughout the condition.

On objective examination of the affected joints there is often very little to be made out, but sometimes the joints are swollen and reddened. As the patients always recover the pathology of the condition is still obscure. It is possible that the synovial membrane is affected in the same way as the skin when we remember that the rash is usually coincident with the joint pains.

There is no record of the joints becoming purulent and there is no case of endocarditis or pericarditis reported as following the condition.

Duration:

In my cases the average duration was 24 hours.

Treatment:

Absolute rest is the most grateful form of treatment, although belladonna or lead and opium fomentations may be applied. I found in one case that cold compresses gave most relief. The salicylates are stated to be useless and considering that one was dealing with a patient convalescent from diphtheria, I did not consider that I was justified in using them.

Illustrative Cases:

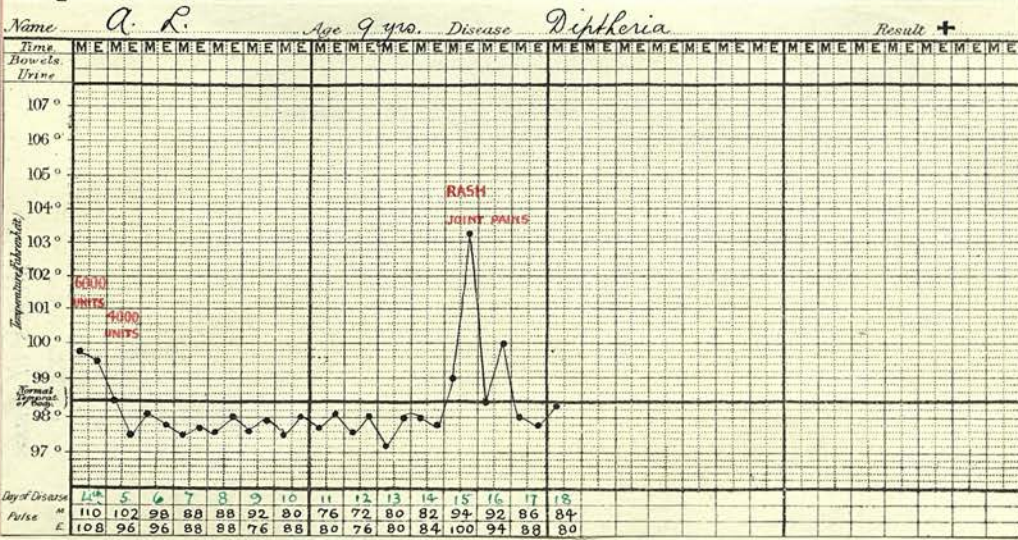
I have already described two cases on pages 31 to 35.

Case III. A.L., aet 9, female.

Was admitted on the fourth day of a well-marked attack of faucial diphtheria, with uvula and soft palate involved. She received 6000 units on admission and 4000 units on the next day.

On the tenth day after injection a morbilliform rash appeared. In the evening her temperature went up to 103.6°, and she complained of pain in both shoulder joints. There was no evident swelling but the joints were very tender. On the next morning the rash was faded but the knee joints were swollen and tender on palpation.

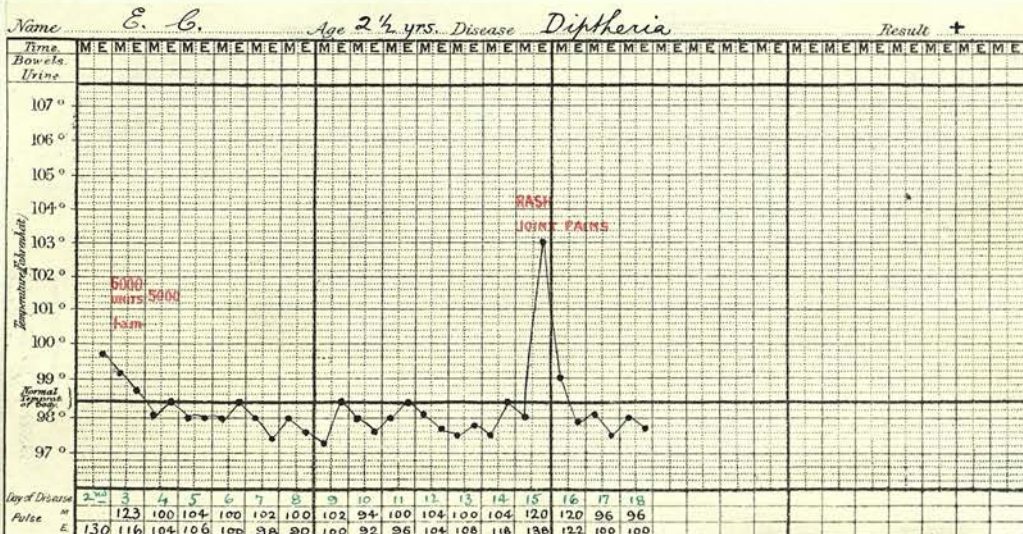
The pain passed off in the course of the day and the patient was completely better by the next morning. She had albumin in her urine for the first time on the day preceding the rash and joint pains.



Case IV. E.C., aet 2½, female.

This child came in very late at night on the second day of an attack of faucial diphtheria. She received 6000 units at 1 a.m. and on the following day as the throat was not improved, she got a further injection of 5000 units.

On the forenoon of the eleventh day after this injection a multiform erythematous eruption came out all over the child. She had then no joint pains. In the evening, however, the elbow-joints were reddened and swollen, and although no other joints were outwardly affected, the child objected very strongly to being moved. The temperature went up to 103° but the condition was quite better the next day and there was no later development of Serum Disease.



Secondary Angina and Adenitis:

It is extremely difficult to say whether a secondary angina or secondary enlargement of glands is due to the serum or to the initial diphtheria. I have only seen two cases, see pages 32-35 & 51 and either of these cases may have been due to the diphtheria, but according to Rolleston, as this occurred coincident with other serum manifestations it may have been due to the injection of the serum.

Albuminuria:

The injection of serum appears certainly to cause albuminuria in some cases. This albuminuria is very transient and lasts only for one or two days. I have observed several cases in which a definite increase occurred in the amount of albumin in a pre-existent albuminuria when the serum rash was present.

No physician would now attempt to treat diphtheria without antitoxin and it is thus impossible to obtain a sufficient number of cases of diphtheria untreated with antitoxin in order to compare the incidence of albumin in the cases which have had antitoxin.

Antitoxin Abscesses:

I have never seen an abscess develop after the injection of serum.

Rolleston reports ten cases and states that they occur usually simultaneously with the urticaria. He considers that they are most apt to occur where a large bulk of fluid has been given.

In my opinion, these abscesses are certainly not due to the antitoxin but simply to the want of careful asepsis in the giving of the injection.

B. SERUM DISEASE FOLLOWING THE USE OF ANTI-STREPTOCOCCIC SERUM.

Marmorek seems to have been the first to produce an anti-streptococcic serum and Chantemesse was the first to report his results with this serum in the treatment of erysipelas. Since then anti-streptococcic serum has been used largely as a therapeutic agent in the treatment of erysipelas puerperal sepsis, cellulitis, and indeed in any streptococcal infection.

The anti-streptococcic serum now usually employed are polyvalent, as it is recognised that "a serum

"prepared with one variety of streptococcus may not immunise against another variety of the organism and it is therefore usual now to immunise the horse with several strains of streptococci, and the serum so obtained is termed a polyvalent or multi-partial one."

Dr Hermann Lenhartz advises against the use of Marmorek's serum for two reasons. He states firstly that he has found the serum to be useless as a therapeutic agent, and secondly, that the most disagreeable after effects may follow the employment of this remedy.

He gives the details of a case of facial erysipelas in a girl of 24 whom he treated with serum in doses of 10 c.c. the total amount of serum used being 50 c.c. spread over three days.

Ten days after the first injection the patient was seized by high fever interrupted by chills, by a general exanthem, and by articular and muscular pains which daily increased in severity and distribution. He affirms that no joint was spared. The intervertebral and the temporo-maxillary articulations also were severely involved. The muscles were tender. On the third day of this period the exanthem was introduced by itching, and diffuse redness of the fingers and hands. On the next day there appeared

dots, wheals and larger areas similar to the eruption of measles. There were severe constitutional symptoms and frequent attacks of diarrhoea for twelve days. Ultimately the patient made a complete recovery.

There is one case of death reported by Hunter who used anti-streptococcic serum in pernicious anaemia, collapse and death following almost immediately upon the injection.

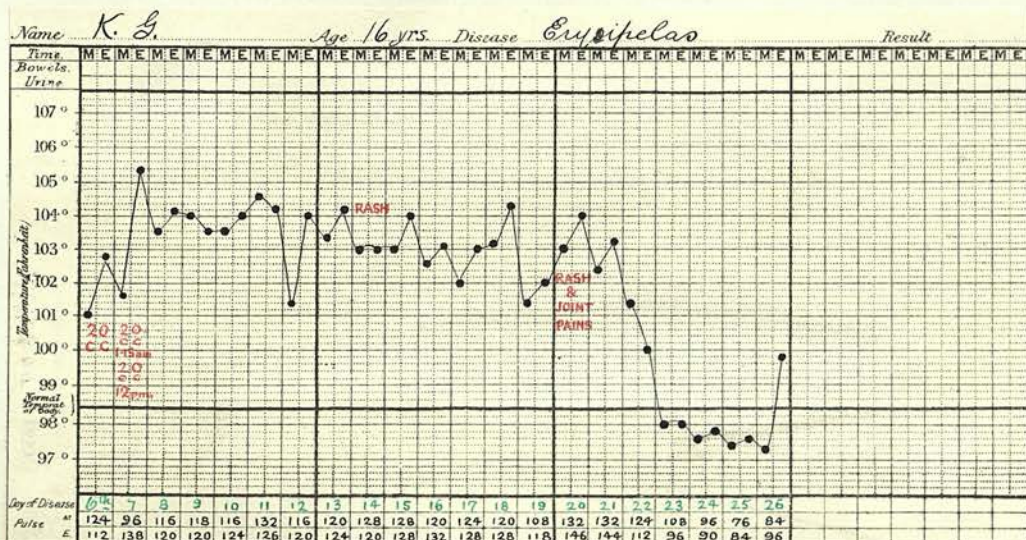
The serum which I used in the six cases here recorded was a polyvalent serum prepared by one of the large, well-known firms. The cases were all cases of pronounced facial erysipelas chosen for serum treatment because of the severity of their attack. I also tried to pick out early cases in order that I might give the serum the best possible chance of effecting a cure.

Only one patient out of the six I treated really suffered any serious discomfort from the effects of the serum. She was a girl of 16 who was admitted on the sixth day of her disease, the erysipelas having apparently been started by her having had her ears pierced. On admission the whole face was very swollen. She was injected with 60 c.c. of serum within twenty-four hours in doses of 20 c.c. She vomited twice about four hours after injection, and sweated

profusely. I did not push the serum owing to the pronounced rise in temperature following upon the last dose.

On the seventh day after injection an evanescent urticarial rash appeared which troubled the girl greatly with a resulting itchiness.

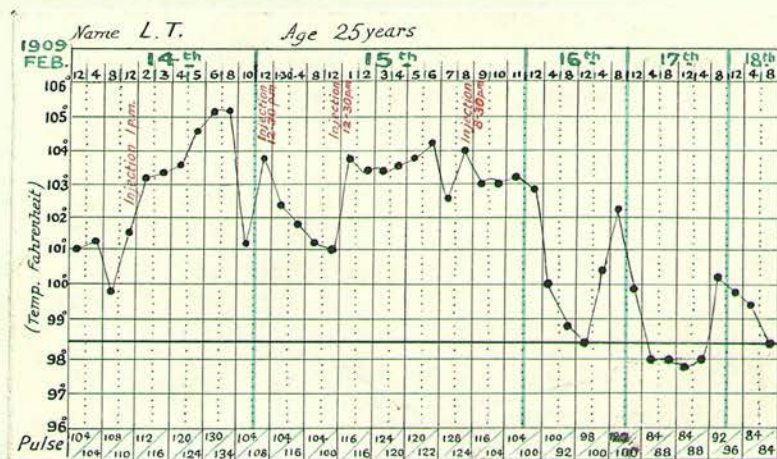
On the eleventh day after the last injection her temperature went up slightly from 103 to 104.6° and a papular eruption manifested itself all over the body. The eruption was morbilliform in colour and came out all over the trunk and limbs, the face, however, being left free. She complained of pains in her right elbow and wrist. The following day these joints were better but the left knee was definitely swollen and very tender on palpation. The rash did not fade until 24 hours later and the knee-joint remained sore for about a day after the rash had disappeared. She had no albumin in her urine on admission to Hospital, but during the course of these serum manifestations albumin was present. I append below her daily chart.



Horse serum being the basis of anti-streptococcic serum, we naturally expect that the serum disease when it manifests itself after the injection of the serum should show the same train of symptoms which follow the use of anti-diphtheritic serum.

Temperature:

Careful observations were made of the effects on the temperature but no definite conclusions can be arrived at. Each case shows variation. In some cases the temperature rose, in others it fell, while in some it remained constant. I append the temperature chart of a patient to whom I gave 110 c.c. in doses of 30 c.c.



Pain at the seat of injection:

The six cases received the injection beneath the skin of the back, below the angle of the scapula. In five of these cases, and including the case of the patient who received 110 c.c. of serum, there was no pain or tenderness complained of. Only one case complained of slight tenderness over the seat of injection, and I consider that in her case the pain was caused by the injection of the serum into the layers of the skin.

Enlargement of Glands:

The lymphatic vessels of the posterior thoracic wall converge to the axillary lymphatic glands. These glands would be the glands one would expect to enlarge following upon the injection of serum. In none of my cases did I find these glands enlarge. In one case the glands in the neck became enlarged during convalescence, but there was a history of previous enlargement of the cervical glands and I think this enlargement was undoubtedly due to tubercle.

Urine:

Oliguria: Oliguria does certainly follow in some cases on the injection of this serum. In one of my cases 16 oz. was the usual amount passed for three

days following the serum, as contrasted with 30, 36 and 40 oz. during her last four days in Hospital.

Albuminuria: Four out of the six cases had albumin in the urine on admission to the Hospital.

The immediate effect of the serum was to reduce in these four cases the amount of albumin. In three cases albumin disappeared altogether after a few days. In one case a trace of albumin persisted all through the patient's stay in Hospital.

In one of the two cases which had no albumin on admission, albumin manifested itself during the time of her antitoxin rash and remained present for six days.

Diazo reaction: This reaction was negative and continued absent right through the disease.

Vomiting:

In my experience of erysipelas I have not found that sickness and vomiting are of common occurrence during the progress of the disease, although of course at the onset of an attack, and as a prodromal symptom vomiting is exceedingly common.

In the notes of these six cases treated with serum I find that three of them vomited, all within

a few hours of the injection. One case also vomited several times during the days on which the antitoxin rash was present.

Rashes:

Four of the six cases had rashes due to the serum. In one case a very evanescent urticaria appeared on the 21st day round both wrist joints, lasting only a few hours.

The patient who received 110 c.c. of serum had a rash on the tenth day from the first injection. The rash was a multiform erythema and came out over the area of injection and spread forward as a blotchy erythema on the abdomen. The face was flushed, and the eyelids puffy and swollen. The arms and legs were covered with a fine scattered erythema, papular in places and urticarial round the knee-joints. This rash was not itchy.

The other two cases which developed rashes had also secondary rashes.

The one started with an urticaria which appeared only for a few hours around the seat of injection on the eighth day following her first dose of serum. On the twenty-fourth day after her first injection a very distinct, discreet, papular eruption came out all over the body and lasted for 48 hours. This rash

was extremely itchy.

The other case gave quite the opposite results. She developed first a papular erythema, which came out on the fourth morning after her first injection. It remained quite bright for two days and spread all over the body.

Nine days from her first injection this patient developed an urticarial rash which passed also all over the body, affecting principally the extensor aspect of the limbs. It lasted for twenty-four hours and curiously enough, did not appear to give the patient any annoyance whatsoever.

Temperature during the rash:

The only patient who had a temperature during the incidence of the rash was the patient whose rash was coincident with her joint-pains. The other cases had no rise of temperature with the coming out of their rashes.

Joint Pains:

Only one of the cases had joint-pains; the right wrist and the right elbow and the left knee were the joints affected. The joints were swollen and tender and remained so for two days. Belladonna fomentations helped, I think, to relieve the pain.

Sex	Age	Dose	Rash	Date from Injection	Joint Pains.
Female	15	80 c.c.	-	-	-
Male	50	60 c.c.	-	-	-
Female	50	80 c.c.	Urticaria	21st day	-
Female	25	110 c.c.	Multiform Erythema	10th "	-
Female	16	60 c.c.	Urticaria Papular Erythema	8th " 14th "	+
Female	14	60 c.c.	Papular Erythema Urticaria.	4th " 9th "	- -

Conclusions:

I cannot state that the Serum really cured any of these cases. The injections may have in some of the cases modified the attack.

The patient who had the largest dose - 110 c.c. - suffered a relapse at the end of three weeks.

Such a large bulk of Serum has to be given that the mere size of the injection must inconvenience the patient.

The manifestations of Serum Disease were not sufficiently alarming to contra-indicate the Serum if the use of it as a curative agent in erysipelas had been more marked.

C. SERUM DISEASE FOLLOWING THE USE OF
INTRA-SPINAL INJECTIONS OF SERUM.

I have been able to watch, in six cases, the effect of intra-spinal injections of serum.

The serum used in five of these cases was Flexner's anti-meningococci serum, and in the other case Ruppel's serum was used.

These six cases were all cases of cerebro-spinal meningitis. I do not include cases of meningitis which on bacteriological investigation were found due to other organisms, e.g. pneumo-coccal cases, as in these cases, only the one injection of serum was given at the first lumbar puncture. I also do not include cases of cerebro-spinal meningitis which died within a short time of admission, as they did not live long enough to give evidence of serum sickness.

Flexner's Serum:

The horse is the animal used in the preparation of this serum also. "The method of immunisation is "by using at first gradually increasing doses of a "vaccine. Later liver cultures are used and the in- "jections are made every seven days. Alternately "with the cultures injections of an autolysate pre- "pared from the diplococcus are made."

Dose of the serum: The dose usually employed was 30 c.c. but if on lumbar puncture 45 or 50 c.c. of cerebro-spinal fluid is drawn off, the dose of the serum was increased to 45 c.c. The injections were usually repeated daily, or even at shorter intervals until distinct improvement was established in the patient's condition.

Effect of injections: The actual injection of the serum usually caused the patients pain. They complained of this pain in the back and the legs. Headache and restlessness would sometimes follow injection, while again the injection of the serum at another time would result in quieting a previously restless patient.

One case who was admitted as a severe case of cerebro-spinal meningitis and who made great progress under treatment until the fifth day in Hospital suddenly collapsed and died, just after an injection of the serum. I consider, however, that his death was due to sudden heart failure seen occasionally in this disease, as he had shown no symptoms of collapse after any of the other previous injections and only the same dose of serum, 30 c.c., was given to replace the 30 c.c. of cerebro-spinal fluid drawn off.

Temperature: The injection was sometimes followed by a marked rise in the temperature, but on other occasions the temperature fell.

Rashes:

Two of these five patients developed urticarial rashes. The case which received the largest dose of serum did not do so.

Age	Dose	Rash	Days in Hospital.	Result.
4	90 c.c.	No Rash	-	Complete cure
28	225 c.c.	No Rash	-	Complete cure
13	120 c.c.	Circinate erythema Urticaria.	3rd 9th	Recovered but left deaf.
2½	165 c.c.	Urticaria	9th	Still in Hospital but doing well.
2½ ¹⁰ / ₁₂	150 c.c.	No Rash	-	Lived five days in Hospital. Died immediately after lumbar puncture and injection of serum.

Illustrative Cases:

Case I., G.S., aet 13, male.

This patient was admitted on the third day of his disease with a history of severe headache,

vomiting and delirium. The illness had started suddenly. On admission the boy was delirious and very restless. He was extremely hyper-sensitive. There was no marked head retraction but his head was rigid. He had a very definite Kernig's sign. There were no haemorrhages.

On lumbar puncture the fluid was found to be under pressure and purulent. I drew off 38 c.c. and injected 30 c.c. of serum. On the next day his condition was much the same and herpes had developed on the lips. He received two injections of 30 c.c. of serum, 10 c.c. and 25 c.c. of cerebro-spinal fluid being drawn off. He was still very restless but he slept well after ten grains of Veronal.

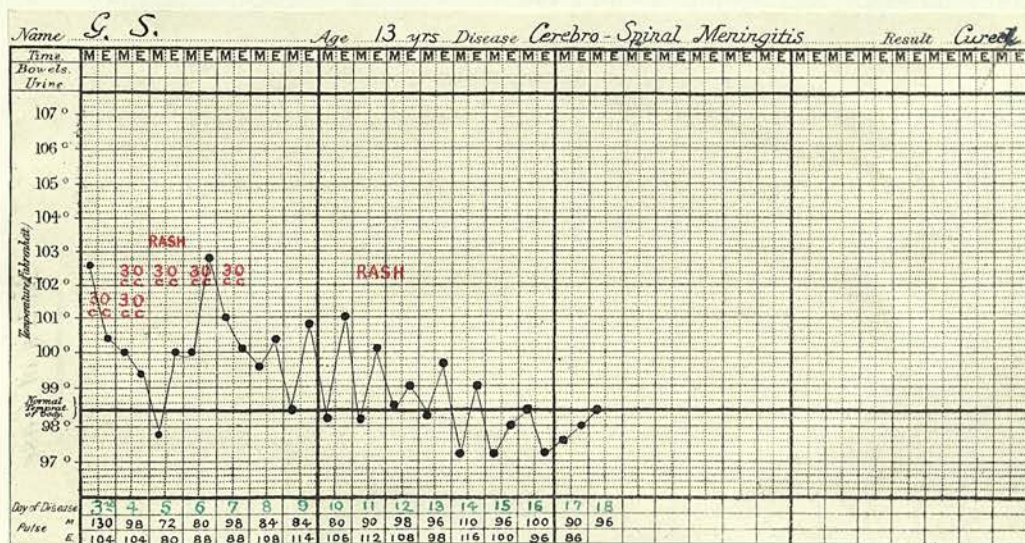
The next morning there were some spots of circinate erythema on his legs while the general condition of the patient was much improved. He was punctured again that day and 30 c.c. of serum given. On the next day the boy was quite conscious but was absolutely deaf. He was punctured again and 45 c.c. of fluid, still slightly turbid, was drawn off, and 30 c.c. of serum injected. On the day following he received his final dose of 30 c.c. of serum while 45 c.c. of a clear, yellowish fluid was drawn off.

He was mentally now quite active, and told us he was anxious to get up. The head rigidity was

gone but Kernig's sign was still present. His improvement was maintained from day to day.

On the fourth day after his last injection and seven days subsequent to the appearance of the circinate erythema an urticarial eruption appeared on the arms and neck. The eruption was very itchy. This rash came out on the trunk and legs next day, and it tended to coalesce round the joints, especially the knee-joints. It lasted for three days.

The patient had not other symptoms of serum sickness and he made a good recovery from the disease, but unfortunately was left deaf.



Case II. B.S., aet $2\frac{1}{2}$, male.

This patient came in on the sixth day of his disease, with a history of sudden vomiting, general pain and shivering. He was unconscious before

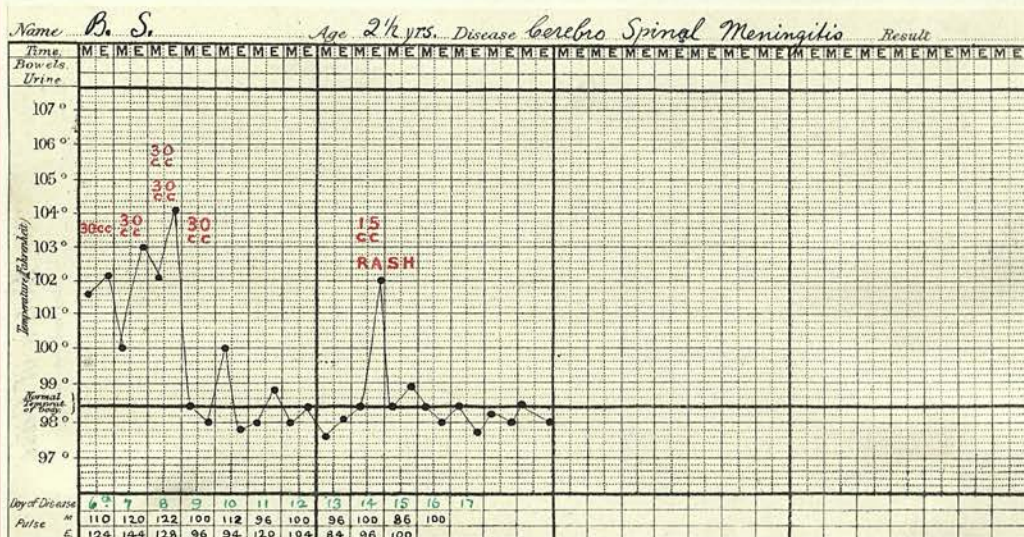
admission, but he was quite conscious on arrival at the Hospital. There was a well-marked Kernig but no head retraction. The head was, however, rigid. The fluid on puncture was turbid and flowed freely. He received 30 c.c. of serum, at the first injection, and 30 c.c. on the next day. He was punctured again at midnight following his second injection, and received 30 c.c. of serum, although 50 c.c. of fluid was drawn off. That same afternoon I punctured again and got no fluid, owing possibly to adhesions. I put in 30 c.c. of serum and his temperature fell to normal. He was then left undisturbed for over 26 hours, when on puncturing I got 50 c.c. of fairly clear fluid which I replaced with 30 c.c. of serum. He made considerable improvement for four days but his Kernig was still well-marked and the head rigidity did not entirely disappear.

On the fifth day from the last injection, a well-marked urticarial rash appeared all over the child. In spite of this evidence of serum reaction, as his condition had not altogether cleared up, I punctured again the day on which the rash came out and got off 35 c.c. of clear fluid, replacing part of it with 15 c.c. of serum.

The result of this injection together with the serum rash, sent the temperature up to 102° but it

came down next morning.

The rash lasted for five days, remaining always urticarial in type, and it showed the usual character of such an eruption, disappearing from one place to appear afresh on another part of the body. The rash was itchy. The general condition of the patient improved and he required no further treatment.



Ruppel's Serum:

I have treated one case of cerebro-spinal meningitis with intra-spinal injections of Ruppel's serum. This serum is in the form of a dry preparation which he recommends should be dissolved in cold, sterilised water, and injected into the spinal canal.

The case I treated was a boy of $3\frac{1}{2}$ years. He had in all 130 c.c. of serum injected in 25 c.c. doses. He did not improve and he has gradually

passed into the chronic state of the disease. He has been already nearly three months in Hospital.

It is, of course, impossible to judge any serum on one case, but even if this serum should prove, on further experience, to be beneficial, I consider there is more risk in using it than in using Flexner. The Flexner Serum is warmed before injection by placing the bottles in hot water, and therefore shock is obviated.

I found in using cold intra-spinal injections that the shock was very marked. This child nearly died on three occasions following injection and required free stimulation.

It is impossible to heat this dissolved serum as it becomes a gelatinous mass which cannot be injected.

GENERAL CONCLUSIONS.

I. Serum sickness is very variable in its manifestations and no definite statement can be laid down as to the time of occurrence of the various phenomena.

II. Such a very small proportion of cases are really inconvenienced at all by any of its symptoms that it is unnecessary to regard its possible development in the treatment of disease by means of serum.

III. The different symptoms described will vary according to the serum used.

IV. Personal idiosyncrasy appears to be an important factor in deciding its occurrence.

V. The only constant manifestations are rashes, of various types, and pain and swelling of different joints, sometimes accompanied by a rise in temperature.

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