# ABNORMAL REACTIONS TO HORSE SERUM IN THE SERUM TREATMENT OF CEREBROSPINAL FEVER.

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In the *Journal of Hygiene* for January, 1907, I noted the effect of repeated injections of horse serum in a number of persons who were for the most part diphtheria patients. Certain of these persons developed abnormal serum reactions, and the view was expressed that the interval of time between the injections of serum was a primary factor in determining these abnormal reactions.

## Introductory.

It will be recalled that the normal serum reaction, the most obvious detail of which is a skin eruption, follows injection of serum after a lapse of time, varying on either side of ten days, which is known as the period of incubation or latent period. The abnormal serum reaction as here understood differs from the normal in its more speedy onset and more rapid course. It is of two forms, the immediate and the accelerated. The immediate form may be local or general, appearing in 24 hours or less. The accelerated form succeeds the injection which causes it after a shorter latent period than in the normal reaction.

Within recent months, the subject in various aspects has been further under consideration, with reference to animals by Rosenau and Anderson (VII. and XI. 1907), Otto (1907), Goodman (VI. 1907) and others, and with reference to man by Goodall (VII. 1907). The conclusions of my paper are in general sustained by Goodall's observations, which likewise relate to diphtheria patients. His earliest immediate reaction after reinjection for diphtheria was 35 days from the initial puncture, a period longer by 24 days than was shown by my plague contact. His

earliest accelerated reaction after reinjection for diphtheria was 25 days after the first injection, a period shorter by 16 days than in my case VII. 86. Goodall further suggests that, in diphtheria, original normal reactions and original large doses predispose to subsequent abnormal reactions.

It is here proposed to note the corresponding serum phenomena which emerged during the treatment of certain cases of cerebrospinal fever. In view of the suggestion referred to later that diphtheria poison plays a contributory part in producing supersensitation of guinea-pigs, it may be profitable to review a series of cases exempt from the influence of that toxin. Further, since the frequency of dosage, and the volume of serum given, in a number of these subjects of cerebrospinal fever, were higher than is customary in dealing with diphtheria, it may be of interest to observe whether there were any corresponding differences in the character of the reactions induced.

## Sera employed.

The four curative sera employed were derived from the horse. The serum first used, Prof. A. Wassermann's, was obtained from the Royal Prussian Institute for Infectious Diseases. The serum which was chiefly employed was prepared by Messrs Burroughs, Wellcome & Co. Messrs Rebman supplied the third of the sera, and the fourth was furnished by Messrs Meister Lucius and Brüning of Höchst am Maine. Large doses and frequent administration were associated with Messrs Burroughs, Wellcome & Co's serum especially, and with Messrs Rebman's serum in less degree. The serum from Höchst was little used for this series of cases, and the doses of Prof. Wassermann's serum which were given were relatively small. So far as serum reactions are concerned the four sera did not show specific differences, and it will not be necessary to distinguish between them in reporting the results of their repeated administration.

## Survey of the cases.

Of the cases of cerebrospinal fever admitted to Belvidere Hospital during parts of 1906 and 1907, 73 were injected with serum on more than one occasion. Of the 73 cases 23 died within 10 days of the first injection, without showing any serum reaction, either normal or abnormal. The 50 remaining cases form the material for these remarks.

The 50 cases had 270 injections in all, an average of 5·4 per head. Twenty-eight of the 50 had more than three injections, 17 had more than five, and six had more than 10. The largest number of injections in a single case was 21. In my earlier paper (I. 1907), among 135 cases of repeated injection for diphtheria, only two had more than three administrations.

The 50 cases received 7958 c.c. of serum in all, an average of 159 c.c. per head. Twenty-three of the 50 had more than 90 c.c. and 12 had more than 200. Six of the cases had each more than half a litre in all, the largest total for a single person being 725 c.c. In my earlier paper (I. 1907), among 135 cases of diphtheria, 33 had more than 90 c.c. These figures are the basis for the statement made above that both as regards frequency and volume of dosage the standard of the 50 cases of cerebrospinal fever was higher than is usual in diphtheria.

Of the 50 cases 36 had subcutaneous injection only; in 13 cases one injection was into the spinal theca, and the remaining injections were subcutaneous; and in one case, one injection was thecal, one intravenous and the remainder subcutaneous. None of the cases furnished a record of previous serum treatment at any time. Twenty-six recovered from the disease.

Of the 50 cases 29 had serum rashes. In 15 of these the normal rash alone appeared. Seven of the patients showed both a normal and an abnormal reaction, and seven had an abnormal reaction only. A normal reaction with or without a following abnormal reaction was thus observed in 22 cases, and an abnormal reaction, with or without a preceding normal reaction, in 14 cases.

### Points for consideration.

In dealing with the influences at work on these cases in producing abnormal reactions, the five following points may be considered:—the total quantity of serum injected; the total number of injections given; the interval between the first injection and the final injection; the presence or absence of an earlier normal reaction; and the quantity of serum administered within the latent period of the normal reaction.

### Quantity of serum.

The dosage in 27 of the 50 cases was 100 c.c. or less, while 23 cases had more than 100 c.c. Of the 27 cases which had 100 c.c. or less, three—or 11·1 per cent.—showed an abnormal reaction, and of the 23

cases which had more than 100 c.c., 11—or 47·8 per cent.—had an abnormal reaction. Of the 27 cases however which had less than 100 c.c. 19 received the last injection within the latent period, and eight beyond it. The three cases of abnormal reaction were all among the eight who received their last injection after the close of the latent period, a fact which suggests that the time between injections was at least as potent in causing abnormal reactions as the volume of serum administered. These relations are maintained in Fig. 1 which shows in diagrammatic form the relative incidence of normal and abnormal reactions in the 50 cases as the quantity of serum administered rises from 50 c.c. to 100 c.c. and thence by gradations of 100 to over 700 c.c. The normal reaction is seen to increase slightly in frequency as the dosage rises: the incidence of the abnormal reaction is irregular and its infrequency in the lower groups, as just stated, is associated with a factor which is related to time rather than volume. Fig. 1 thus fails to show that increase of the total quantity of serum given induces a corresponding increase in the frequency of abnormal reactions.
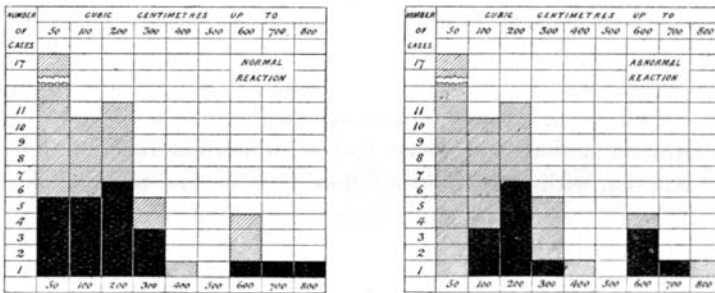


Fig. 1.

## Number of injections.

The number of injections given to 33 of the 50 cases was five or less, while 17 had more than five injections. Of the 33 cases which had five injections or less, three—or 9 per cent.—exhibited an abnormal reaction, and of the 17 cases which had more than five injections 11—or 64·7 per cent.—were cases with an abnormal reaction. Frequency of administration however cannot with certainty be regarded as determining an abnormal reaction if the interval of time between the effective injection and the injection which immediately precedes is partly within and partly without the latent period of the normal serum

reaction, counted from the first injection of all. If, for example, in any particular case a series of injections be given within 10 days of the first injection, and if the series of injections be followed at a later date by another injection which induces an abnormal rash, it may well be that this result is not due to frequency of injection but to the circumstance that the final injection took place beyond the latent period of the normal reaction. This statement affects alike cases with five injections or less and cases with more than five injections. Of the 33 cases which had five injections or less, three—Nos. 1, 26, and 34—had abnormal reactions. In all three the interval between the effective injection and the injection immediately preceding it was partly within and partly without the latent period of the normal reaction. Of the 17 cases which had more than five injections 11 had abnormal reactions. Three cases of the 11—Nos. 12, 32 and 36—had an interval similar to the above. In the remaining eight—Nos. 7, 10, 11, 17, 21, 28, 31 and 40— the interval between the effective injection and the injection immediately preceding was entirely without the average latent period. In three of these cases—Nos. 21, 31 and 40—the interval was demonstrably without the actual latent period, as the close of the latent period in each case had been marked by a normal reaction. Case 21 which had six injections within the latent period, had the first abnormal reaction after the tenth injection; case 31 which had three injections within the latent period had the abnormal reaction after the seventh injection; and case 40 which had six injections within the latent period had the first abnormal reaction after the ninth injection. In certain cases therefore by continuing to inject, an abnormal reaction may at length be obtained, after preceding administrations outwith the latent period have failed to induce it. That is to say that in certain cases the number of injections is a factor in determining abnormal reactions.

The number of injections in the 50 cases is arranged in diagrammatic form in Fig. 2, which shows the relative incidence of normal and abnormal reactions respectively as the number of injections increases from two to over 20. There is no evidence from the diagram that the frequency of the normal reaction increases with the number of injections of serum. The preponderance of abnormal reactions in the higher groups is to be looked on as subject to the reservation above noted regarding the coincidental influence of the latent period. The most that can be said is already stated, so far as these cases are concerned; under certain conditions the number of injections is a factor in inducing abnormal reactions.

## *Interval of time.*

When the 50 cases are considered with special reference to the interval of time between the first injection of all and the injection which induced an abnormal reaction if an abnormal reaction was induced, or the last injection given if no abnormal reaction occurred, the importance of this interval, already referred to incidentally, comes clearly under notice. In 24 of the 50 cases there was a period of 10 days or less between the first injection and the injection which induced an abnormal reaction, or the last injection given if no abnormal reaction occurred. In 26 of the cases the corresponding period was over 10 days. Of the 24 cases within the 10 day interval none had abnormal reactions. Of the 26 cases beyond the 10 day interval, 14—or 53·8 per cent.—had abnormal reactions.
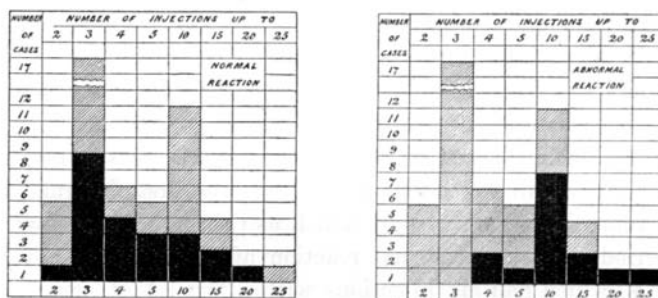


Fig. 2.

The intervals between the first injection of all and the injection which led to an abnormal reaction, or the last injection given if no abnormal reaction occurred, are arranged in diagrammatic form in Fig. 3, which shows the relative incidence of normal and abnormal reactions as the intervals lengthen from two days to over 60. The normal reaction is seen to be constant throughout the groups. It has no apparent relation to the length of the interval under consideration; in many cases it occurred in the course of it. The abnormal reaction on the other hand is absent from the columns showing intervals up to two and ten days respectively. It first appears in the column with intervals between 11 and 20 days, but it will be noted that it shows no definite tendency to increase in frequency as the intervals lengthen further. These observations accord with the results of my previous paper. They suggest that the primary condition for an abnormal reaction is the

apse of a certain interval of time, but that further lapse of time beyond his interval has no additional influence in inducing the phenomenon. The interval in question which is approximately ten days is the latent period of the normal reaction.
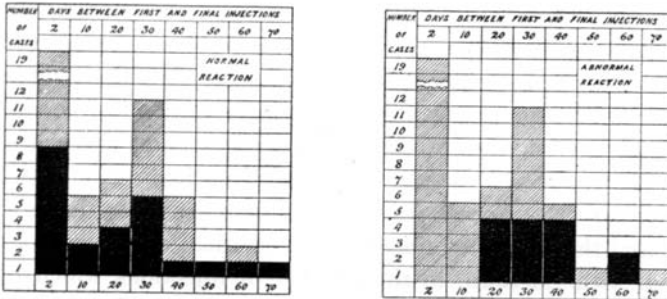


Fig. 3.

## Preceding normal reaction.

As already noted Goodall (VII. 1907) has suggested that a patient who has had a serum reaction at a primary attack of diphtheria is more likely than a patient who has not had such a reaction to develop an abnormal reaction after re-injection for a second attack. Corresponding relations for the 50 cases of cerebrospinal fever are shown in the following:

Table 1.

| Normal reaction | Abnormal reaction | | Total |
|---|---|---|---|
| | Present | Absent | |
| Present | 7 | 15 | 22 |
| Absent | 7 | 21 | 28 |
| | | | 50 |

Of 22 cases with a normal reaction at the first, seven—or 31·8 per cent. —furnished an abnormal reaction at a later period. Of 28 cases which did not exhibit a normal reaction at the first, seven—or 25 per cent.— had a normal reaction subsequently. The difference between these percentages is in the sense of Goodall's conclusion: it is however too slight to have significance.

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### *Preceding large doses of serum.*

Goodall has also indicated that the greater the quantity of serum administered during the primary attack of diphtheria, the more likely is an abnormal reaction to occur after serum for a second attack. While Goodall's patients received the injection of serum which led to an abnormal reaction on account of a relapse or second seizure of diphtheria, the corresponding doses for the 50 cases now under notice were given in the routine treatment of a single attack of cerebrospinal fever, or on account of oscillations in its course, and therefore do not lend themselves to an equally ready classification. The close of the latent period of the normal reaction has thus been selected as a line of division, and the presence or absence of abnormal appearances has been considered with reference to the number of injections which occurred within the period in question. Table 2 shows the incidence of abnormal reactions as the number of injections within the latent period rises from one to seven. The cases however are unequally divided among the groups and no deduction seems justified.

#### Table 2.

| Number of injections of serum within the latent period | Abnormal reaction | | Total |
|---|---|---|---|
| | Present | Absent | |
| 1 | 2 | — | 2 |
| 2 | 1 | 6 | 7 |
| 3 | 8 | 26 | 34 |
| 4 | — | 1 | 1 |
| 5 | 1 | 2 | 3 |
| 6 | 2 | — | 2 |
| 7 | — | 1 | 1 |
| Total | 14 | 36 | 50 |

That the 50 cases do not definitely support Goodall's view that original normal reactions and original large doses predispose to subsequent abnormal reactions is possibly a consequence of the smallness of the numbers involved: it will however be recalled that Otto and Rosenau and Anderson (IV. 1906) have published experiments to the effect that guinea-pigs which have been used for standardising purposes, and which have for that reason been injected with horse serum and diphtheria toxin together, are more prone to furnish abnormal reactions in response to following injections of serum than guinea-pigs which have been treated for experimental objects with normal horse serum alone. Such experiments suggest to Otto, and also to Lewis (1908),—though Rosenau

and Anderson in a later paper (VII. 1907) do not entirely concur—that diphtheria toxin plays a part in sensitizing animals to the serum of animals of another species; and it is matter for speculation whether diphtheria patients, containing as they do in their bodies the poison of that disease, may not be more favourable subjects for abnormal serum phenomena than persons who are suffering from cerebrospinal fever. Several observers have already commented on the neutral qualities of the anti-meningococcic sera, so far as specific serum effects are concerned. Wassermann (1907), for example, dealing with 102 cases which were treated with serum, for the most part in repeated doses, reports appearances of the nature of nettlerash in five examples only.

The prevailing severity of cerebrospinal fever may also be adduced as a cause for the slight proportion of abnormal reactions in cases which had showed normal reactions at the first. Although there was no special mortality among cases which had a normal reaction at the first and no abnormal reaction later, yet many who ultimately recovered were in the extreme of illness during the period when abnormal reactions were possible, and their exhausted condition at that time may well have had an influence in suppressing the reactions in question.

### Details.

Since any value which may attach to these remarks must depend on the interpretation which has been placed on the reactions shown by the cases, details are added relating to the reactions in question. Most of the facts are suitable for arrangement in tabular form and are so arranged in Table 3. The abnormal reactions of individual cases are separately described. In the table and in the text $S_1$ means the first injection of serum, $S_2$ the second injection, and so on for higher numbers.

#### Details of abnormal reactions.

*Case* 1. *Accelerated reaction* following $S_3$, $S_4$ or $S_5$ on 6th, 5th, or 4th day. A slight urticaria of one day's duration as opposed to the two days' duration of the preceding normal rash.

*Case* 7. *Immediate reaction*, thrice. *First* after $S_{10}$ on 52nd day, an area of erythema appearing 30 minutes after injection, measuring 12 cm. in diameter, and lasting 2 hours. *Second.* After $S_{11}$ on 53rd day, an area of erythema appearing 15 minutes after injection, measuring 12 cm. in diameter and lasting $2\frac{1}{2}$ hours. *Third.* After $S_{12}$, on 54th day, an area of erythema appearing 15 minutes after injection, measuring 2 cm. in diameter, and lasting $1\frac{1}{2}$ hours. A gradual diminution in the activity of the reaction, as if $S_{10}$ and $S_{11}$ had each neutralized a certain

TABLE 3. *Details.*

| Serial | Sex | Age | Death † | Total amount of serum, c.c. | Number of injections | S₁ | S₂ | S₃ | S₄ | S₅ | S₆ | S₇ | Later injections in order | Normal reaction — Day of onset | Normal reaction — Character | Abnormal reaction — Day of onset | Abnormal reaction — Character |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 3 | + | | 2 | 1 | 4 | | | | | | | | 0 | 34 | Accelerated |
| 2 | F | 3 | | | 6 | 1 | 3 | 9 | 18 | 19 | 20 | | | | 0 | | 0 |
| 3 | M | 6 5/12 | | | 4 | 1 | 2 | 3 | 26 | | | | | | 0 | | 0 |
| 4 | F | 8 | + | | 12 | 1 | 18 | 19 | 40 | 41 | 42 | 44 | 45, 46, 52, 53, 54 | 9 | Urticaria. Duration 2 days | | 0 |
| 5 | M | 16 | + | | 8 | 1 | 2 | 3 | 26 | 31 | | | | | (very faint) | | 0 |
| 6 | F | 6 | + | | 3 | 1 | 3 | 3 | | | | | | | 0 | | 0 |
| 7 | F | 11 | + | | 6 | 1 | 2 | 3 | | | | | | | 0 | 52, ? | Immediate |
| 8 | F | 1 3/4 | + | | 9 | 1 | 2 | 15 | 33 | 34 | 35 | | | 9 | Erythema. 12 hours' duration | | 0 |
| 9 | M | 19 | + | | 9 | 1 | 2 | 3 | 32 | 33 | 34 | 40 | 41, 42 | | 0 | | 0 |
| 10 | M | 10 | | | 9 | 1 | 2 | 3 | 7 | 8 | 9 | 18 | 19, 20 | | 0 | 33, ? | Immediate |
| 11 | F | 2 | | | 2 | 1 | 2 | | | | | | | | 0 | 35, 4 | Immediate |
| 12 | F | 17 | | | 4 | 1 | 3 | 3 | | | | | | | 0 | 1 | Immediate |
| 13 | F | 23 | + | | 3 | 1 | 4 | | | | | | | | 0 | | 0 |
| 14 | M | 8 | + | | 4 | 1 | 4 | 9 | 29 | | | | | 9 | Erythematous and morbilliform, preceding S₃. Oedema and intermissions, lasting 16 days. Temp. 103·2°. | | 0 |
| 15 | F | 4 2/3 | | | 3 | 1 | 2 | 3 | | | | | | 7 | Morbilliform, severe, lasting 3 days. Temp. 104°. | | 0 |
| 16 | F | 7 | + | | 3 | 1 | 2 | 3 | | | | | | | 0 | | 0 |
| 17 | F | 16 | + | | 21 | 1 | 2 | 3 | 11 | 12 | 13 | 16 | 17, 18, 22, 23, 24, 29, 30, 31, 35, 36, 37, 40, 41, 42 | 14 | Erythema. Lasting 2 days. | 33 | Accelerated |
| 18 | M | 3 | | | 3 | 1 | 2 | 3 | | | | | | | 0 | | 0 |
| 19 | M | 1 4/6 | + | | 7 | 1 | 2 | 3 | 17 | 18 | 19 | 27 | | | 0 | | 0 |
| 20 | M | 21 | + | | 3 | 1 | 2 | 3 | | | | | | | 0 | | 0 |
| 21 | F | 3 | | | 13 | 1 | 2 | 3 | 9 | 10 | 11 | 21 | 22, 23, 32, 33, 34, 44 | 15 | Urticaria, severe, lasting 3 days. | 32, 33 | Immediate |
| 22 | F | 10 | + | | 6 | 1 | 2 | 3 | 24 | 25 | 26 | | | | 0 | | 0 |
| 23 | M | | | | 3 | 1 | 2 | 3 | | | | | | | 0 | | 0 |

| No. | Sex | Age | | Dose | | | | | | | | | Ref. Nos. | Remarks | Day | Reaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | M | 16 | | 300 | 6 | 1 | 2 | 3 | 8 | 10 | 11 | | | Erythema and urticaria, lasting 4 days | 7 | 0 |
| 25 | M | 3 | + | 150 | 5 | 1 | 2 | 4 | 30 | 67 | | | | Fugitive erythema, lasting 2 days, followed on 9th day by urticaria of 3 days' duration, and on 28th day by slight erythema | 3 | 0 |
| 26 | M | 5 | | 125 | 4 | 1 | 2 | 3 | 26 | | | | 2 | Fugitive erythema, lasting 2 days | 26 | Immediate |
| 27 | F | 1½ | | 75 | 3 | 1 | 2 | 3 | | | | | | 0 | | 0 |
| 28 | M | 16 | + | 250 | 6 | 1 | 2 | 3 | 26 | 27 | 28 | | 7 | Local erythema, lasting 6 hours | 28 | Immediate |
| 29 | M | 9 | | 80 | 4 | 1 | 2 | 3 | 25 | | | | | 0 | | 0 |
| 30 | M | 13 | | 225 | 3 | 1 | 2 | 3 | 19 | | | | 9 | General urticaria, lasting a few hours | 0 | Immediate |
| 31 | F | 2 | + | 175 | 7 | 1 | 2 | 3 | 23 | 27 | 59 | | 9 | Urticaria of 2 days' duration, followed on 16th day by urticaria of one day's duration | 60 | Immediate |
| 32 | F | 3 | + | 135 | 6 | 1 | 2 | 3 | 20 | 22 | 25 | | 8 | General urticaria, lasting 3 days | 21, 23 | Immediate |
| 33 | F | 1½ | + | 110 | 5 | 1 | 2 | 3 | 18 | 23 | | | 7 | General urticaria, lasting 2 days, followed on 14th day by urticaria lasting 12 hours | | 0 |
| 34 | F | 2 | + | 85 | 4 | 1 | 2 | 4 | 20 | | | | 8 | Local urticaria lasting 3 days, followed on 14th day by general urticaria, lasting 1 day | 21 | Immediate |
| 35 | F | 2⅚ | + | 175 | 5 | 1 | 2 | 4 | 14 | 15 | 33 | | | 0 | | 0 |
| 36 | F | 7½ | + | 150 | 6 | 1 | 2 | 3 | 31 | 32 | | | | 0 | | Accelerated |
| 37 | M | 19 | | 225 | 3 | 1 | 2 | 3 | | | | | 19, 25, 26, 33, 34 | General urticaria, lasting 5 days. Temperature 102° | 36 | 0 |
| 38 | M | 10 | | 600 | 12 | 1 | 2 | 3 | 4 | 8 | 9 | 10 | 25, 26, 28, 40, 43 | 0 | | 0 |
| 39 | M | 25 | + | 725 | 12 | 1 | 2 | 3 | 9 | 18 | 19 | 20 | 15, 18, 19, 20, 26, | Local urticaria, lasting a few hours | | 0 |
| 40 | M | 2½ | + | 645 | 16 | 1 | 2 | 3 | 5 | 7 | 8 | 14 | 29, 34, 37, 38 | General urticaria, lasting 6 days | 18, 21 | Immediate |
| 41 | M | 20 | | 250 | 5 | 1 | 1 | 2 | 3 | 5 | | | | Erythematous and morbilliform, lasting 10 days. Submaxillary, parotid and cervical adenitis. | | 0 |
| 42 | M | 26 | | 325 | 3 | 1 | 2 | 3 | | | | | | 0 | | 0 |
| 43 | F | 31 | | 60 | 3 | 1 | 2 | 3 | | | | | | Arthritic pains of shoulders and elbows | | 0 |
| 44 | M | 3 | + | 30 | 3 | 1 | 2 | 3 | | | | | | Urticaria of 24 hours' duration | | 0 |
| 45 | F | 4⅚ | + | 30 | 3 | 1 | 2 | 3 | | | | | | 0 | | 0 |
| 46 | F | 16 | | 20 | 2 | 1 | 3½ | | | | | | | 0 | | 0 |
| 47 | F | 16 | + | 60 | 3 | 1 | 2 | 3 | | | | | | 0 | | 0 |
| 48 | F | 3½ | | 30 | 3 | 1 | 2 | 3 | | | | | | 0 | | 0 |
| 49 | M | 4 | | 30 | 3 | 1 | 3 | 4 | | | | | | 0 | | 0 |
| 50 | F | 5 | | 40 | 4 | 1 | 3 | 4 | 25 | | | | | Erythema of 2 days' duration | 8 | 0 |

proportion of a specific antibody present when $S_{10}$ was given. A fall in the precipitating power of the blood of a somewhat similar character is referred to by Nicolle and Abt (II. 1908). Compare case 21. Preceding injections negative.

*Case* 10. *Immediate reaction, thrice. First* after $S_4$ on 33rd day, an area of erythema appearing 30 minutes after injection, measuring 20 cm. in diameter and lasting 12 hours. *Second.* After $S_5$ on 34th day, the same as the above. *Third.* After $S_6$ on 35th day, also the same as the above. Preceding injections negative.

*Case* 11. *Immediate reaction, thrice. First* after $S_6$ on 35th day, an urticaria appearing within 24 hours of injection and lasting 6 hours. *Second,* after $S_8$ on 41st day, an area of erythema appearing 15 minutes after injection, measuring 10 cm. in diameter and lasting one hour. *Third,* after $S_9$ on 42nd day an area of erythema, appearing 10 minutes after injection, measuring 10 cm. in diameter and lasting $1\frac{1}{2}$ hours. Preceding injections negative.

*Case* 12. *Immediate reaction.* After $S_7$ on 18th day, a general urticaria, appearing several hours after $S_7$ and lasting 4 hours.

*Case* 17. *Accelerated reaction.* Severe articular pain in shoulders on 33rd day, two days after $S_{15}$, and again articular pain in legs on 44th day, two days after $S_{21}$. The shoulder arthritis suggests an accelerated reaction : the character of the leg arthritis is less definite.

*Case* 21. *Immediate reaction* four times after a normal reaction on 15th day. *First* after $S_{10}$ on 32nd day, an erythema appearing immediately after injection measuring 14 cm. in diameter and lasting four hours. *Second,* after $S_{11}$ on 33rd day an erythema appearing immediately after injection measuring 12 cm. in .diameter and lasting $4\frac{1}{2}$ hours. *Third,* after $S_{12}$ on 34th day, an erythema appearing immediately after injection, measuring 4 cm. in diameter and lasting 5 hours. *Fourth,* after $S_{13}$ on 44th day, an erythema, appearing 30 minutes after injection, measuring 2 cm. in diameter and lasting $4\frac{1}{2}$ hours. Gradual diminution in activity of reaction. Compare case 7. Preceding injections negative.

*Case* 26. *Immediate reaction,* succeeding a reaction on 2nd day which has been taken as normal. After $S_4$ on 26th day, redness, swelling and tenderness of the whole abdomen, appearing from 2 to 3 hours after $S_4$ and lasting about 12 hours.

*Case* 28. *Immediate reaction,* on 28th day, after $S_5$ but before $S_6$, a general urticaria, appearing within 24 hours of injection, and lasting 24 hours.

*Case* 31. *Immediate reaction.* A normal reaction occurred on the 9th and 16th days as stated in Table. $S_4$ was on the 19th day and was followed on the 20th day by a general morbilliform rash of 24 hours' duration. $S_5$ was on the 23rd day and was attended by a general morbilliform rash of three days' duration. These morbilliform eruptions may have been continuations of the normal reaction, but $S_7$, which was given on the 59th day, was followed within 24 hours by an erythema which affected the whole trunk : at the same time the abdominal wall became hard and swollen. This manifestation which lasted 1 day had the character of an immediate reaction.

*Case* 32. *Immediate reaction* twice, succeeding a normal reaction on 8th day. *First,* on 21st day following $S_4$ an abdominal urticaria, appearing within 24 hours of

injection and lasting 12 hours. *Second,* after $S_5$ on the 23rd day an urticaria of abdomen and legs, appearing within 24 hours of injection, and lasting 12 hours. Accepted as immediate reactions.

*Case* 34. *Immediate reaction.* Succeeding a normal reaction on 8th day. A general urticaria appearing on 21st day, within 24 hours of $S_4$ and lasting one day.

*Case* 36. *Accelerated reaction.* On 36th day, three days after $S_6$ an abdominal urticaria.

*Case* 40. *Immediate reaction,* twice, succeeding normal reaction on 9th day. *First,* after $S_9$ on 18th day, general erythema appearing about 12 hours after injection and lasting six hours. *Second* after $S_{11}$ on 21st day, general erythema appearing within 24 hours of injection, and lasting one day; reappearing again on the 24th day, and lasting again for one day. Accepted as immediate reaction.

## *Theoretical Note.*

In my earlier paper (I. 1907) I had suggested that a secondary antibody might play a part in the reactions which follow the injection of extraneous sera, inasmuch as the toxic product, which resulted from the interaction of a substance contained in the serum injected and of an antibody which it originated, might evoke a secondary antibody which combined with the toxic product, controlled its effects and ultimately brought the reaction to a close. The latent period of the secondary antibody was to be regarded as shorter than that of the primary antibody. In the normal reaction the various processes were gradual. In one of the forms of the abnormal reaction the case was otherwise; in the immediate abnormal reaction the primary antibody produced by the first injection of serum persisted at the time of the second injection, but the secondary antibody, evoked by the toxic product of the first injection of serum with the primary antibody, had already vanished from the system. When therefore the antibody-producing substance of the second injection of serum reacted with the primary antibody produced in the organism by the first injection of serum, the abruptly liberated toxic material exerted its hurtful influence unchecked until sufficient time had elapsed to admit of the preparation anew of a secondary antibody to control its effects.

Discussing this suggestion in connection with supersensitation Goodman (VI. 1907) expresses the view that, although it may account for the phenomena occasioned by repeated injections of serum, it cannot hold for the corresponding phenomena elicited by *diphtheria toxin.* That the suggestion, which deals with a substance that is bland at the time of injection,

is not appropriate to the effects of the diphtheria poison which is toxic at the time of injection may be readily admitted, but it must at the same time be maintained that Goodman's alternative theory, if relevant as regards supersensitation by diphtheria toxin, cannot be looked on as applicable to serum rashes. In terms of the side-chain hypothesis Goodman states that the injection of small doses of toxin leads to the destruction of certain sessile receptors and the sympathetic degeneration of others, so that vital cells are left more open to attack. Be this as it may for diphtheria toxin, there seems no occasion to suppose that reactions of supersensitation to extraneous sera have any special relation to sessile receptors of the cells of vital organs. In my earlier paper I spoke of sessile receptors in this connection. The data then seemed somewhat equivocal. Recently however more definite evidence has become available. Rosenau and Anderson (VII. 1907) have confirmed a statement previously made by them (IV. 1906) as to the congenital supersensitiveness of the young of supersensitized female guinea-pigs,—an indication that the active substance, to some extent at least, is free in the maternal blood. Vaughan and Wheeler (VI. 1907) have referred to a similar condition in the young of animals supersensitized to egg albumen. Otto (1907) has shown that extracts of the organs of supersensitized guinea-pigs do not modify the action of horse serum on other supersensitized animals, and both Otto and Friedemann (1907) have been able to induce passive supersensitation by injecting the serum of supersensitized animals. The general sense of these observations is that the active substance is not attached to cells in vital organs but is free in the blood of animals. There is therefore reason to think that the reactions under discussion are related less to sessile receptors of vital cells than to free receptors. The experiments cited are concerned with immediate reactions of animals; it is probable by analogy that similar conditions obtain in the human subject.

Interest also attaches to the question of a secondary antibody in the light of papers by Nicolle and Pozerski (I. 1908) and Nicolle and Abt (II. 1908). Nicolle and Abt hold that *two antibodies* play a part in serum reactions, but both antibodies in their view are primary. Though each antibody is active at a different time from the other, both are called into existence by the original dose of the extraneous material. One of the antibodies is an albuminocoagulin—or precipitin;—the other is an albuminolysin, a conception on the analogy of cytolysin. With reference to albuminocoagulin, though precipitation is not effected

within the living body, it is held that there takes place in the body a coagulation or condensation of the foreign albumen, a process by which its potential activity is lessened. Albuminolysin, again, becomes active after albuminocoagulin : it dissolves the compound of extraneous serum and albuminocoagulin and liberates a poison of the nature of endotoxin, a class of substance, as Wolff (1904) pointed out, against which the animal body has no defence. Hence the action of albuminolysin is injurious.

According to Nicolle and Pozerski (I. 1908) large doses of extraneous serum evoke albuminocoagulin; while small doses favour the production of albuminolysin. Large doses therefore should tend to mild serum reactions, and small doses to severe reactions. In animal experiments this holds good: Otto and Rosenau and Anderson (VII. 1906) have found that initial small doses are more dangerous to guinea-pigs than initial large doses. In the human subject however the reverse appears to obtain: von Pirquet and Schick (1905) and Goodall (VII. 1907) assert that in man large doses of serum are more active than small in predisposing to abnormal reactions.

With further reference to the theory that the predominance of one or other of two primary antibodies determines the nature of abnormal reactions; since albuminocoagulin—or precipitin—in excess leads to mildness or abeyance of abnormal reactions while albuminolysin in excess predisposes to their severity, it might have been expected that animals or persons whose blood was found to contain precipitin would have their serum reaction mild or absent, while those whose blood was free from precipitin would show an active response. Such an association however has not been proved to exist. On the contrary, from experiments reported by von Pirquet and Schick (1905), it would appear that there is no definite relationship between precipitin formation and the serum reaction : they do not accompany one another of necessity, nor does the pressure of one imply the absence of the other. There are therefore points in the theory that two primary antibodies determine serum reactions, which are difficult to reconcile with the facts under notice.

The work of Vaughan and Wheeler (VI. 1907) with egg-albumen has a reference to the possibility of a *secondary antibody* under conditions analogous to those of the serum reaction. These observers have split egg-albumen in vitro into two portions, of which one was bland when injected into animals, and the other toxic. Both the bland portion, and entire egg-albumen itself, proved capable of sensitizing

Wheeler interpret in the sense that a material evoked by the non-toxic portion splits entire egg-albumen within the body and liberates a toxic substance which is allied or identical with the toxic extract produced in vitro. Repeated injections of the toxic extract induced some increase of the resistance of animals to it. Though the attempt to detect an antibody has failed, as Vaughan and Wheeler state, yet acquired resistance to what is probably a proteid substance suggests to the mind antibody formation. The toxic substance derived by the cleavage of egg-albumen in vivo, being similar to that obtained in vitro, may be presumed to react in a similar manner and to evoke a similar antibody.

On this analogy the toxic substance which manifests its presence by serum rashes and the like, and which is to be regarded as liberated by the action on extraneous serum of an antibody to that serum, may be expected to lead to the formation of another antibody, secondary in the sense that it is not elaborated in direct response to an antibody-producing material in the serum injected but in response to a toxic product of the reaction of that original antibody-producing material with an antibody which it gives rise to after injection.

### *Summary.*

The following general statements are applicable to the 50 cases of cerebrospinal fever which have been under notice here.

The total volume of serum given did not affect the frequency of abnormal reactions.

The total number of injections of serum, in certain cases, may have been a factor in inducing abnormal reactions.

The interval of time between the injections concerned was the primary influence in determining abnormal reactions.

It was not apparent that a preceding normal reaction predisposed to a subsequent abnormal reaction.

It was not apparent that a large administration of serum within the latent period predisposed to a subsequent abnormal reaction.

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