

ON THE SUPERSENSITATION OF PERSONS BY HORSE-SERUM.

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Dr J. R. Currie's interesting and instructive article in the January, 1907, number of the *Journal of Hygiene* induces me to publish a short account of certain cases that have come under my observation at the Eastern Fever Hospital. They afford additional information to that given in his paper.

Most of those who have had more than a scanty experience of the antitoxin treatment of diphtheria, are familiar with the phenomena of supersensitisation as they manifest themselves in the human subject. It is some years now since I became acquainted with them. At first I was inclined to attribute the symptoms to some peculiarity of the serum employed; but subsequent observations showed that this view was incorrect, and that the essential factor in their production appeared to be a fresh injection of serum after an interval of some duration (weeks or months).¹ I sent an account of three well-marked cases of what is now termed the "immediate reaction" to the Committee of the Clinical Society which was investigating the claims of the antitoxin treatment of diphtheria at the time; but the report of that Committee was in the press, and so the notes of the cases were published in the appendix to the report without comment². I have since met with a few similar cases, which are included, with those reported to the Committee of the Clinical Society, in Table I.

As von Pirquet and Schick and Dr Currie have shown, and as has been observed experimentally in animals, it is not the number of injections of serum that is of importance, but the length of time that

¹ See *Encycl. Medica*, Vol. III. p. 18.

² See *Clin. Soc. Trans.* Vol. XXXI.

elapses between the first injection or series of injections (extending over a few days), and the second injection or series of injections. My cases afford some evidence as to the length of this interval. At the Eastern Hospital patients have repeatedly been injected with serum on two, three, four or more occasions on successive days¹; and I have never had any reason for supposing that the serum phenomena were earlier in their onset in consequence. This view is supported by Dr Currie's observations; though he does suggest that the later injections of a series may determine the appearance of a rash which would otherwise have remained undeveloped. To convert this suggestion into a certainty, or to disprove it, requires the analysis of a larger number of cases than he gives. The appearance of a rash on the fifth day after a single primary injection is by no means uncommon; and it is still less uncommon on the sixth or seventh days. Hence if injections are given in any particular cases daily for a week, and a rash appears on the sixth or seventh day, it cannot be certain that its appearance has been determined by any of the later injections.

There is also another fact which makes the question more difficult of solution, and it is one to which Dr Currie does not refer; namely, that one single injection may produce two (and on rare occasions even three) distinct rashes (*e.g.* urticaria and erythema circinatum) separated by a definite interval in which there is no rash nor other serum phenomena. Cases 31, 47, 54 and 74 in Table I are examples of this. (See also the Clinical Society's Report.) The explanation of this fact that has offered itself to me is the mixing of the sera of two or more horses in order to obtain a serum of an antitoxic value that is between the two extremes. It is customary to attribute the occurrence of a reaction largely to the idiosyncrasy of the patient injected; but the idiosyncrasy of the horse which supplies the serum has certainly to be considered, with regard both to the frequency and character of the rashes. The fact that different sera will produce different serum-phenomena was noticed by the late Dr J. W. Washbourn, Mr A. H. Card and myself in the first series of cases of diphtheria that were treated with serum in this country². I think it is not unreasonable to assume that if the serum of one horse gives rise mostly to urticaria (which is usually somewhat early in its appearance compared with *E. circinatum*), and of another mostly to *E. circinatum*,

¹ I have notes of a few cases in which patients received up to eight injections of serum within a few days without any hastened serum-reaction, sometimes without any reaction at all. One patient received 200 c.c. in eight injections during 11 days, and had no reaction.

² *Clin. Soc. Trans.* Vol. xxxiii.

then a mixture of the two may as the result of a single injection produce the one rash followed at a distinct interval by the other. (Case 3 of Dr Currie's series may be thus explained.) So that the practice of mixing sera vitiates the conclusions that might be drawn as to the manifestation and time of occurrence of rashes from an analysis of cases in which there had been several injections on successive days.

One thing, however, appears to be certain, that it is extremely unusual for serum-phenomena to manifest themselves within three days of a single injection or the first of a series of injections (provided that the patient has never had serum some weeks, months, and occasionally even years before). My experience on that point quite confirms that of Dr Currie as shown in diagram B in his paper. But if the patient has had one or more injections of serum some considerable time previously, then he may get a serum-reaction earlier than usual.

Now the cases that present an interval, usually of some length, between two injections or series of injections, are those in which the patients are treated with serum for a relapse or second attack of diphtheria (or suspected diphtheria), after having been treated with serum in the first attack. I happen to have at hand the notes of all such cases that occurred at the Eastern Hospital during the years 1897, 1898 and 1899, and 1904, 1905 and 1906. The following table, Table I, gives the essential particulars of these cases. As there are some differences between them, the two series are distinguished in the table. Those against which the words "second series" are placed in Column VIII belong to the years 1904, 1905 and 1906, the rest belong to the years 1897, 1898 and 1899.

The cases, 90 in number, are arranged according to the length of time that elapsed between the primary attack and the relapse or second attack, beginning with the case that had the shortest interval.

In Column I are put the numbers applied to the cases for the convenience of reference.

In Column II is stated the number of injections of serum given for the primary attack; and the days on which the injection or injections were given. The days are reckoned from the first injection, *i.e.* the first day is the day of the first injection. Thus in case 4, 1, 2, 4, mean that one injection was given on the first day (usually the day of admission to hospital), one the day after, and one three days after. One injection was given each day, except in cases 89 and 90.

In Column III are given the times of occurrence and nature of any serum-reaction caused by the injection for the primary attack. Thus

TABLE I.

I	II	III	IV	V	VI	VII	VIII	IX
1	1	None; but see Col. VI	8	—	11, rash; 12, joint-pains (?)	—	—	F. 16
2	1, 3	8, rash	16, 17, 18	—	19, rash	—	—	M. 3
3	1	—	16	—	—	—	Second series	M. 2
4	1, 2, 4	—	18	—	—	—	—	F. 7
5	1	—	18, 22	—	—	—	—	M. 6
6	1	—	19, 20	—	—	—	—	M. 3
7	1, 2	7, rash	19	—	—	—	—	F. 6
8	1	—	23	—	—	—	—	M. 12
9	1	11, rash	23, 24	—	—	—	—	F. 11
10	1	—	24	—	—	—	—	F. 5
11	1	8, rash	25	—	26, rash	—	—	F. 2
12	1	7, rash	26, 27	—	27, joint-pains; 30, rash	37, rash	—	F. 37
13	1	—	27	—	—	—	Second series	M. 2
14	1, 2	—	28	—	—	—	Second series	M. 16
15	1	9, rash	30	—	32, rash	—	—	M. 8
16	1	—	30	—	—	—	Second series	M. 1
17	1	—	31, 36	—	—	—	—	M. 1
18	1	10, rash	32	—	33, rash	—	Second series	F. 4
19	1	9, rash	34	—	—	—	—	F. 2
20	1	—	34	—	—	—	Second series	M. 1
21	1	—	34	—	—	—	Second series	F. 10
22	1, 2	—	35	—	—	—	Second series	M. 7
23	1	10, rash; 12, joint-pains	36	Rash within an hour	41, rash	—	Second series	M. 2
24	1	—	36	—	—	—	Second series	F. 3
25	1, 2, 3	11, rash	38	20 mins., rigor, convulsions; T., 105° F.	39, rash; 42, rash	—	—	F. 5
26	1	8, rash	38	30 mins., rigor; T., 105° F.	39, rash	—	—	F. 6
27	1	—	40	1 hour, rash	—	46, rash	Second series	F. 5
28	1	—	41	—	—	—	Second series	F. 2
29	1	—	42, 43, 44	—	—	—	—	M. 10
30	1	13, rash	42	6 hours, rash; T., 104° F.	—	48, rash	—	M. 3
31	1	5, rash; 8, rash	42	slight shivering at once; 6 hours, rash	44, joint-pains	49, rash & joint-pains	Second series	F. 23
32	1	16, rash	45	—	46, rash; 50, rash	—	Second series	F. 2
33	1	10, rash	46, 47, 48	—	51, convulsions (?)	—	The relapse of diphtheria began with a severe rigor	M. 2

I	II	III	IV	V	VI	VII	VIII	IX
34 1					48, rash		Second series	M. 2
35 1	10, rash	46		3½ hours, rash		54, rash	Second series	M. 4
36 1, 2	8, rash	48			50, rash	56, rash	Second series	M. 4
37 1, 2	19, rash	49				56, rash; 59, local abscess	Second series	F. 2
38 1		49						F. 2
39 1		50, 51			51, rash and collapse before 3rd injection			F. 3
40 1, 2, 3, 4		51		15 mins., rash & vomiting; 2½ hrs. rigor		57, rash		M. 6
41 1, 2, 3, 4	16, rash	51		1 hour, rash, vomiting, rigor				F. 3
42 1	13, rash	52				58, rash		M. 1½
43 1, 2, 3	9, rash and joint-pains	52				58, rash		F. 43
44 1, 2		53						F. 9
45 1		53						M. 11
46 1		54				60, rash		F. 4
47 1	4, rash; 15, rash	54		30 mins., rash & collapse		60, rash		F. 2
48 1	12, rash	55		2 hours, rash			Second series	F. 6
49 1		55			58, rash	62, rash		F. 6
50 1		57				64, rash	Second series	F. 2
51 1		57			68, rash			F. 7
52 1, 2	10, rash; 19, rash	58, 66		1 hour after 3rd injection (68th day), rash				F. 1
53 1		59		15 mins., rash, T. 103° F., vomiting	61, rash	65, rash	On the 42nd day the nasocord antitum was opened under chloroform. On the 55th day there were convulsions, followed by a rash. The organisms on trachea and kidneys, cause unknown	F. 9
54 1	12, rash; 15, rash	59						M. 2
55 1		59					Second series	M. 3
56 1	10, rash; 13, joint-pains	60				68, rash	Second series	M. 2
57 1	10, rash	63			67, rash	69, joint-pains	Second series	M. 3
58 1, 2	9, rash	64 (2 lots at interval of a few hrs.)			65, rash; 69, rash			M. 4
59 1, 2, 3		64, 66						M. 5

TABLE I (continued).

I	II	III	IV	V	VI	VII	VIII	IX
60	1, 2	—	65	—	—	—	Second series	F. 3
61	1	15, rash	67	—	69, rash	—	—	F. 6
62	1, 2	—	68	—	74, rash	74, rash	—	F. 5
63	1	4, rash	70	—	74, rash	—	—	F. 4
64	1, 2	10, rash	70	—	73, rash	—	—	M. 6
65	1, 3	—	72	1½ hrs., rigor, col-lapse, T. 103.6°F.	—	78, rash	—	M. 4
66	1	—	72	—	78, rash	—	—	F. 9
67	1, 2	7, rash	75, 76	At once after each of the 4th & 5th injections, a rash	—	—	—	F. 5
68	1, 2, 3	—	75, 76	—	—	—	—	M. 10
69	1, 2	—	77	—	—	—	—	F. 3
70	1, 2	11, rash	78	—	—	—	Second series	F. 3
71	1, 2, 3, 4	10, rash	80	3½ hours, rash	84, rash	—	—	F. 3
72	1	—	85	—	—	—	Second series	F. 2
73	1	—	93	—	—	—	Second series	F. 11
74	1	9, rash; 16, rash	94	—	—	—	—	F. 6
75	1	—	97	—	—	—	—	F. 5
76	1	—	102	—	—	—	—	F. 5
77	1, 2	—	111	—	—	—	—	M. 8
78	1	—	113	—	—	—	Second series	M. 2
79	1, 2	—	123	—	—	—	—	M. 2
80	1	—	139	—	—	145, rash	Second series	F. 4
81	1	13, rash	145	—	—	152, rash	—	M. 4
82	1, 3	9, rash	154	—	155, rash	—	—	F. 4
83	1	—	207	—	—	215, rash	—	F. 2
84	1	—	308	2 hours, rash	309, rash	—	Second series	M. 1
85	1	7, rash	364	—	—	370, rash and joint-pains	—	M. 5
86	1	8, rash	387	—	388, rash	393, rash; 396, rash	Second series	F. 3
87	1	6, rash	416	—	417, rash	—	Injected again for 3rd attack of diphteria on 47th day; rash all round seat of injection next day	F. 5
88	1, 2	—	529	—	533, rash	—	Second series	M. 1
89	1 (2 lots at inter-val of a few hrs.)	7, rash and local abscess	1165	—	1169, rash	—	Second series	M. 5
90	1 (2 lots at inter-val of a few hrs.)	—	1511	—	1512, rash	—	Second series	F. 5

Note.—Cases 16, 20, and 83 were doubtfully diphteria at both the first and second attack. Cases 18, 47, 52 and 85 had diphteria at the first attack, but not at the second attack. Cases 88 and 90 did not have diphteria at the first attack, but did have it at the second.

in Case 7, Column III, "7, rash" means that a rash came out on the seventh day (six days after the first injection).

In Column IV is stated the day on which serum was given for a relapse or second attack, reckoning the first day to be that on which the first injection was given for the primary attack. One injection was given on each day except in case 58, where two injections were given at an interval of several hours on the 64th day.

In Column V are shown the time of occurrence and nature of any "immediate reaction," that is a reaction taking place within twelve hours of the first injection for the relapse¹.

In Column VI are given the dates of occurrence and nature of "accelerated reactions," that is reactions appearing from twelve hours to five days after the first injection for the relapse.

In Column VII are given what may be termed the normal reactions occurring after the injection for the relapse, that is rashes or other symptoms appearing on the sixth or later day from the first injection.

Column VIII is reserved for notes on some of the cases.

In Column IX are given the sex and age of the patient. The age is the age at the time of the primary attack.

It will be observed that in only four of the cases did the reaction due to serum in the primary attack occur within five days of the first injection, within the time, that is to say, of an "accelerated reaction," viz. :—cases 47 (third day after the injection), 63 (ditto), 31 (fourth day), and 87 (fifth day). In all these four cases there was only a single injection. The second attack in case 47 was attended with an "immediate reaction," in case 63 with no reaction, in case 31 with both an "immediate" and an "accelerated reaction," and in case 87 with an "accelerated reaction."

The *Immediate Reaction*. In 17 instances, 18·8 per cent., there was an "immediate reaction." Taking the two series of cases separately it will be found that for the first series of cases, 55 in number during the years 1897 to 1899, the percentage was 23·6; and for the second series, 35 during 1904 to 1906, 11·7; there being 13 cases of this reaction in the first and four only in the second series.

In no instance did an "immediate reaction" commence later than six hours after the injection of serum. There are 22 cases in which the serum treatment for a relapse was resorted to before the 35th day after the first injection in the primary attack, and in not one of them did an

¹ I have not seen an abnormal reaction take place between 6 and 19 hours after an injection; hence I have taken 12 hours as the limit of an "immediate reaction."

"immediate reaction" occur. The earliest instance of this reaction was observed in a patient who was again injected 35 days after the primary injection; the latest in a patient injected 363 days after. But it will be noticed that 16 of the 17 cases of "immediate reaction" occurred in patients who were reinjected 35 to 79 days after the primary injection.

The number of cases is small; but so far as they go the figures show that a person who is submitted to a second serum-treatment within five weeks of the commencement of the first, is not likely to suffer an "immediate reaction." The "immediate reaction" may present severe symptoms. Dr Currie does not appear to have witnessed a case of this sort himself, though he alludes to cases that have been recorded by others; case 25 had a rigor followed by convulsions; case 65 a rigor followed by collapse; cases 26, 31, 41 and 42 a rigor; and case 47 collapse; that is seven of the 17 cases certainly presented severe symptoms. In case 25 the symptoms were very severe. Cases 25, 26 and 41 are the three cases recorded in the Appendix to the Clinical Society's Report. Even when the "immediate reaction" consists of a rash only, the rash is prone to be severe and accompanied by a high temperature. All these cases recovered. In case 68 the patient twice had an "immediate reaction."

As has been stated instances of "immediate reaction" have been less frequent of recent years. The dosage (by volume) of serum was rather larger in the second than in the first series of cases. But I should not be justified in assigning this as a cause of the diminished frequency of the reaction.

Though I have a very extensive experience of serum treatment, I have never seen an "immediate reaction" of any kind after a first injection for a primary attack of diphtheria; and I have never seen convulsions, a rigor, or vomiting due to serum except as part of such a reaction, with the possible, but very doubtful, exception of case 33. Only once do I remember to have seen collapse in connection with serum-phenomena apart from an "immediate reaction," and that was in a case of "accelerated reaction," case 39. Rigors are very uncommon in diphtheria.

The *Accelerated Reaction*. I have placed a ? against two of the instances recorded in Column VI, cases 1 and 33. The rash and joint-pains observed in case 1, ten and eleven days after the first injection may very well have been and most probably were due to it. In two other instances I have seen joint-pains as part of an "accelerated reaction," cases 12 and 31; but I have never seen them as part of an "immediate

reaction." In case 33 the relapse was a severe one and began with a violent rigor lasting for twenty minutes; four hours later an indefinite and transient erythema was noticed on the trunk. Antitoxin was not given till four days after the relapse begun, and it was given on three successive days. The convulsions came on three days after the last injection, and proved fatal. There was no rash. Convulsions, usually fatal, are occasionally seen in severe diphtheria, whether treated or not with antitoxin; in most instances they appear after a few days' illness. I do not think, therefore, that in case 33 they were in any way due to the serum.

Excluding these two cases there were 30 cases of "accelerated reaction," 33·3 per cent. The proportion was higher in the second than in the first series, 37·1 per cent. as against 30·8 (13 in 35 and 17 in 55).

The shortest period between an injection for a relapse and an "accelerated reaction," is one of 19 hours, case 86. In every case except one, case 23, the reaction occurred before the fifth day; in 17 cases (including case 86) it appeared the day after; in 5, two days after; in 2, three days after; in 5, four days after; and in 1, five days after. The earliest instance of this reaction after the first injection in the primary attack was 18 days, case 2 (possibly the reaction was due to this injection); the latest occurred 1511 days after, case 90. This reaction usually presents itself as a rash, with or without pyrexia. In one case there was collapse; and in two joint-pains.

In eight instances the "accelerated" had been preceded by an "immediate reaction."

Rarely is the "accelerated reaction" severe; but in all the instances the rash was more than local; except in the third attack in case 87 (not reckoned in the statistics).

The *Ordinary Reaction after injection for a relapse.* (Column VII.) In 24 instances there was a serum-reaction on the sixth day or later after the first injection for a relapse. It is a curious fact that in 15 of the 24 the reaction occurred on the sixth day, that is rather earlier than the ordinary reaction is usually seen after a first injection for a primary attack. Six of the remaining nine cases occurred on the seventh day, two on the eighth and one on the twelfth. In 15 of the cases there had been an "immediate" or an "accelerated reaction."

Thus though there is a distinct break between the extraordinary ("immediate" and "accelerated") and the ordinary reactions, most of the former occurring on the same day as, or on the day after, the reinjection for the relapse and most of the latter on the sixth and seventh

day after, yet even the ordinary reactions appear in these cases to be hastened when compared with the ordinary reactions after the injection of serum in a primary attack. Indeed it might be stated that there are two varieties of "accelerated reaction," one occurring about five days later than the other.

Connection between the occurrence of an "immediate" and an "accelerated reaction" and any serum-incidents of the primary attack. Of the 90 cases 41, 45·5 per cent., had a serum-reaction after the injection given for the primary attack. The percentage of cases with reaction following one injection is 43·3, and following more than one, 50·0. The following table (Table II) shows the relation between the occurrence of an "immediate" or an "accelerated reaction" or both and of a reaction after the serum given in the primary attack.

TABLE II.

	Immediate reaction	Accelerated reaction	Imm.+acc. reaction	No reaction	Total
No reaction after primary attack	2	7	1	39	49
Reaction " " "	7	15	7	12	41
Total	9	22	8	51	90

There was an "immediate" or an "accelerated reaction," or both, in 20·4 per cent. of the cases in which there had been no reaction after the serum given for the primary attack; whereas there was an abnormal (*i.e.* "immediate" or "accelerated") reaction in 70·7 per cent. of the cases in which there had been a reaction at the primary attack.

The following table (Table III) shows the relation between the occurrence of an "immediate" or an "accelerated reaction" and the amount of serum given in the primary attack. During the years under consideration, in both series of cases, serum was given by the 1000 units in varying volume; but it may safely be stated that the larger the number of injections the larger the volume of serum given. During the years 1904, 1905 and 1906 the dosage (by volume as well as by unit) was larger than during the years 1897, 1898 and 1899; but the frequency of injections was less.

TABLE III.

	Immediate reaction	Accelerated reaction	Imm.+acc. reaction	No reaction	Total
One injection	6	11	4	37	58
More than one injection	3	11	4	14	32
Total	9	22	8	51	90

There was an abnormal reaction in 36·2 per cent. of the cases in

which one injection had been given at the primary attack; whereas the percentage was 56.2 in cases in which more than one injection had been given.

The following table (Table IV) shows the relation between the occurrence of an abnormal reaction in a relapse, and the number of injections and occurrence of a reaction at the primary attack.

TABLE IV.

	Abnormal reaction	No abnormal reaction	Total
One injection followed by } reaction	18; 66.6 per cent.	9; 33.4 per cent.	27
One injection not followed } by reaction	6; 17.3 ,,	28; 82.7 ,,	34
Two or more injections } followed by reaction	11; 73.3 ,,	4; 26.7 ,,	15
Two or more injections } not followed by reaction	4; 28.5 ,,	10; 71.5 ,,	14
Total	39	51	90

The figures in these tables, though small, go to show that, given an interval of three to five weeks between primary attack and relapse, if a patient has had more than one injection of serum and had a reaction in the primary attack, he is more likely to get an abnormal reaction of some sort if treated with serum in a relapse than is the patient who has had less serum and no reaction in the primary attack.

Summary.

1. There were 90 patients at the Eastern Hospital, who, during the years 1897, 1898, 1899, 1904, 1905 and 1906, were injected with horse-serum for a second attack or relapse of diphtheria, who had been treated with horse-serum at the first attack.

2. Of these 9 had an "immediate reaction," 22 an "accelerated reaction," and 8 had both, 39 in all, or 43.4 per cent.

3. The "immediate reaction" showed itself a few minutes to six hours after the first injection for the second attack.

4. The shortest interval between the first injection at the primary attack and the occurrence of an "immediate reaction" after a reinjection for a second attack was 35 days; the longest was 363 days.

5. The "accelerated reaction" showed itself 19 hours to five days after the first injection for the second attack.

6. The shortest interval between the first injection at the primary attack and the occurrence of an "accelerated reaction" after a reinjec-

tion for a second attack was 25 days; the longest was 1511 days. In each of these cases the reaction occurred the day after the reinjection.

7. In seven of the cases of "immediate reaction" the symptoms were severe. In all save one of those of "accelerated reaction" they were mild or moderate.

8. In 24 of the cases there was a normal serum-reaction after the reinjection for the second attack; but even this occurred in most cases slightly earlier than is usual after injection at a primary attack.

9. So far as the figures go they show :

(a) that when a patient has had a serum-reaction at the primary attack, he is more likely to have an abnormal reaction after injection at the second attack ;

(b) that the greater the volume of serum given in the primary attack, the more likely is an abnormal reaction to occur after serum at the second attack ;

(c) and that consequently an abnormal reaction is most likely to occur after serum at a second attack when the patient has had a large volume of serum followed by a reaction at the first attack.

There are, however, indications that the volume of serum given at the primary attack may have different effects as regards the determination of an "immediate" or an "accelerated reaction," according to its amount.