LOCALIZED ANAPHYLACTIC INTOXICATION IN CHILDREN FOLLOWING THE REPEATED INJECTION OF ANTITOXIN.*

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V. Pirquet and Schick[1] in their admirable monograph on the "serum sickness" have described the untoward effects of single and of repeated injections of horse serum (antitoxin) in human beings. The cutaneous irritative symptoms which occur six to ten days after a primary injection are known to be dependent on the individual animal that has furnished the serum rather than on any particularly hypersusceptible condition of the patient. Of far greater academic interest as well as of striking clinical importance is the "accelerated" or "immediate" (beschleunigte) reaction which these authors have described. This reaction occurs primarily in patients that have been "sensitized" by a previous serum injection which may have been given months before; it does, however, also occur in certain instances in cases which are given serum for the first time. This accelerated reaction is characterized by the appearance within a few hours, and frequently within a few minutes, of some or all of the following symptoms: malaise, rise of temperature, urticaria or erythema, edema, cyanosis, dyspnea, and at times sudden death.

The results of v. Pirquet and Schick have been confirmed and amplified in a considerable series of cases by Goodall and by Currie. Goodall[2] found that of ninety cases of diphtheria that received two injections of serum, nine showed an immediate reaction on second injection. The time between injections varied from thirty-five to three hundred and sixty-three days. Currie[3] found that the second injection produced some symptoms in as many as sixty-six per cent of one hundred and fifteen cases examined. This author further emphasized the necessity and importance of a time interval between injections.

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The work of the past three years by Otto, Rosenau and Anderson, Gay and Southard, Besredka, and others on serum anaphylaxis in the guinea-pig has thrown much light on the mechanism of the serum sickness in human beings. Little if any doubt remains as to the perfect analogy of the two phenomena. It will be recalled that guinea-pigs that have received a small dose of horse serum will after a proper incubation period react violently to a second dose. The symptoms are first irritative then paralytic, and death, which occurs regularly when proper dosage and incubation period are observed, is always due to cessation of respiration. The cessation is due to overstimulation of an irritable respiratory center and not to its paralysis (Gay and Southard[4]). The symptoms of dyspnea and cyanosis in the severer human cases follow in detail the symptoms of guinea-pig anaphylactic intoxication, and death, when it occurs in man, is likewise due to cessation of respiration. It has further been remarked by Gillette[5] and others that those patients which react to a *primary* injection of serum are almost invariably afflicted with asthma, which disease may reasonably be attributed to some abnormality in the respiratory center. The further analogy between serum anaphylaxis in man and in guinea-pigs in respect to the effect of frequent doses of serum and the importance of the length of incubation periods between doses, on the symptoms involved, will be later considered.

As we have seen, the immediate systemic reaction following a second dose of horse serum in human beings corresponds to the intoxication in guinea-pig anaphylaxis. There has been, however, a form of reaction to alien serum in animals of which the human analogue has not yet been described. Arthus[6] some years ago described the occurrence of local aseptic necroses in rabbits that had been given several subcutaneous injections of horse serum at week intervals. The animals showed no reaction at the point of inoculation after the first three injections of five cubic centimeters each of serum. The fourth injection gave a white infiltrated area, the fifth a still further induration which took

five or six days to resorb, and the sixth injection gave rise to actual necrosis. The point of inoculation in the successive doses is not the same. In rabbits this local reaction is much more constant than a systemic reaction, which may, however, follow a second or third dose when given intravenously. This local reaction was also found by Arthus in guinea-pigs, rats, and doves. In guinea-pigs its occurrence bears no direct or necessary relation to the occurrence of generalized symptoms (Lewis[7]).

We have found that this localized lesion of anaphylactic intoxication (Arthus' phenomenon) occurs frequently in children that have received two or more doses of antitoxin at frequent intervals. The frequency of occurrence of this local lesion varies directly with the number of injections.

It is a routine practice in the Children's Hospital to give the patients one thousand five hundred units of antitoxin (about five cubic centimeters) on their admission and to repeat the dose every twenty-one days so long as the child remains in the hospital or in the convalescent home which is connected with the hospital. The local reaction which we have noticed has occurred as early as the second injection and in some cases not until the sixth injection. The reaction appears within a few hours as a general swelling or edema of the whole region surrounding the point of injection; there is general reddening with marked local calor; this area soon becomes quite glazed and shiny, there is extreme tenderness, and if immediate local treatment, consisting of absolute rest with application of either heat or cold, is not instituted, the process goes on to moderately general tissue necrosis. As the swelling subsides under treatment the region becomes quite markedly indurated and hard, the tenderness and induration often continuing for one or two months, especially immediately about the point of injection.

In the following table, comprising a review of one thousand consecutive cases, are summarized the immediate symptoms both local and general which followed the injection of antitoxin. The table is divided in accordance with the serial case numbers.

TABLE I.

Immediate reactions following injections of antitoxin in children.

Case No.	No. of Injection.	Generalized Symptoms.					Local.
		Temperature.	Malaise.	Edema.	Rash.	Dyspnea.	
1	1st	101.2	Moderate.				
2	1st	101					
3	1st	Slight.			Marked.		
4	2d						In back (necrosis).
5	2d	101					
6	2d	Slight.					In thigh.
7	2d		Marked.		Urticaria.		
8	2d		Marked.				In back.
9	2d	Moderate.	Arthralgia.				
10	2d						Arm, marked.
11	2d						Arm, moderate.
12	2d	Slight.			Slight.		
13	2d		Marked, vomited.				
14	2d	105					Arm, marked.
15	2d						Thigh.
16	2d						Thigh.
17	2d	103			Urticaria.		Moderate.
18	2d						Thigh, moderate.
19	2d	102.5					Back.

2	2d	103					Thigh.
20	2d	101			Moderate.		
21	2d				Urticaria.		
22	2d						Thigh.
23	2d	103					Moderate.
24	2d	101					
25	2d		Marked, vomiting, very restless.	Marked, of face.	Urticaria.		
26	2d		Very marked.				
27	2d	102					
28	2d	101					Marked.
4	3d	Marked.	Marked.		Urticaria.		Back.
29	3d	Moderate.					Moderate.
30	3d	102.2					Right thigh, moderate.
15	3d						Thigh.
17	3d				Moderate.		Back.
19	3d	101					Thigh, moderate.
31	3d						Moderate.
2	3d	103.6	Quite sick.				
32	3d	Slight.					Thigh, moderate.
33	3d	Moderate.					Thigh, moderate.
34	3d						Moderate.
35	3d	102.2	Irregular pulse.				
36	3d	101			Moderate.		
37	3d	Marked.					Arm, marked.
38	3d	100			Moderate.		

TABLE I. — *Continued.*

Case No.	No. of Injection.	Generalized Symptoms.					Local.
		Temperature.	Malaise.	Edema.	Rash.	Dyspnea.	
4.....	4th	Moderate.	.....	.....	Moderate.	.....	Back.
39.....	4th	.....	.....	.....	.....	.....	Back, moderate.
40.....	4th	103	Irregular heart.				
17.....	4th	.....	.....	.....	Urticaria.	.....	Marked.
19.....	4th	101	.....	.....	.....	.....	Thigh, moderate.
32.....	4th	.....	.....	.....	.....	.....	Moderate.
33.....	4th	.....	.....	.....	.....	.....	Moderate.
41.....	4th	Slight.	.....	.....	.....	.....	Slight.
42.....	4th	.....	.....	.....	.....	.....	Slight.
35.....	4th	.....	.....	.....	.....	.....	Moderate.
37.....	4th	.....	.....	.....	.....	.....	Marked.
24.....	4th	.....	.....	.....	.....	.....	Moderate.
43.....	4th	Marked.	.....	.....	.....	.....	Moderate.
4.....	5th	.....	Less than 4th.	.....	Slight.	.....	Quite marked.
44.....	5th	102.8	Quite upset.	.....	.....	.....	Moderate.
39.....	5th	.....	.....	.....	.....	.....	Moderate.
40.....	5th	.....	Marked.	.....	.....	.....	Necrosis.
45.....	5th	.....	.....	General, especially of face.			

17.....	5th	.....	.....	.....	.....	.....	Marked.
19.....	5th	100.6	.....	.....	.....	.....	Moderate.
2.....	5th	103	Quite sick.	.....	.....	.....	Thigh, very marked.
33.....	5th	103.4	.....	.....	.....	.....	Thigh, very marked.
41.....	5th	.....	.....	.....	.....	.....	Thigh, moderate.
42.....	5th	.....	.....	.....	.....	.....	Back, moderate.
43.....	5th	.....	.....	.....	.....	.....	Marked.
4.....	6th	.....	.....	.....	.....	.....	Arm, very marked.
44.....	6th	Moderate.	.....	.....	Moderate.	.....	Arm, very sore; glands in axilla.
40.....	6th	.....	.....	.....	.....	.....	Arm, very sore.
45.....	6th	.....	.....	General, marked.	.....	.....	Thigh, marked.
46.....	6th	Moderate.	.....	.....	.....	.....	Moderate.
2.....	6th	102.4	Slight.	.....	.....	.....	Very marked.
41.....	6th	.....	.....	.....	.....	.....	Moderate.
42.....	6th	.....	.....	.....	.....	.....	Thigh, moderate.
47.....	6th	.....	.....	.....	.....	Marked.	Arm, moderate.
48.....	6th	.....	.....	.....	.....	Moderate.	
49.....	6th	.....	Irregular heart.	.....	Moderate.	Moderate.	Slight.

To summarize the findings in this table:

Following a primary injection in one thousand cases only three (.03 per cent) gave any immediate reaction. The reactions in these three cases were general but very slight and confined principally to slight rises in temperature. They may scarcely be regarded as instances of the same reaction that occurs on reinjection.

Following a second injection in two hundred and eighty-one cases, twenty-six reacted (8.8 per cent). Of these twenty-six, ten gave only generalized symptoms, seven both generalized and local and nine local symptoms only.

Following a third injection in one hundred and three cases fifteen reacted (14.5 per cent). Of these fifteen two showed only generalized symptoms, nine both generalized and local, and four local symptoms alone.

Following a fourth injection in thirty-six cases, thirteen reacted (27.75 per cent). Of these thirteen two showed generalized symptoms alone, three both general and local, and eight localized only.

Following a fifth injection in twenty-five cases, twelve reacted (42.9 per cent). Of these twelve one only was with generalized symptoms, five with generalized and local symptoms, and six with pure local symptoms.

Following a sixth injection in fifteen cases, eleven reacted (seventy-four per cent). Of these eleven only one showed pure generalized symptoms, four both general and local, and six purely local.*

It is evident, then, that the occurrence of immediate reactions on reinjections with antitoxin varies directly with the number of injections given. Our local reaction of intoxication, moreover, increases gradually over the systemic or generalized reaction of v. Pirquet and Schick in proportion to the number of injections given at three-week intervals.

This latter fact, moreover, corresponds perfectly with the conditions in animals. In Arthus' experiments rabbits were

* It may be noted that there were twenty-eight children under a year old who received two or more injections. Of these eight were injected three times, four were injected four times, and one was injected five times. In none of these cases was any reaction obtained.

given relatively large doses of serum at short intervals and showed the local reaction invariably but the general reaction seldom. In guinea-pigs the successful demonstration of the generalized reaction depends on a small initial dose and a relatively long incubation period; the period of incubation varies, indeed, directly with the number of moderate doses or the size of a single initial dose (Gay and Southard[8]). In guinea-pigs, moreover, the local reaction is unusual. V. Pirquet and Schick, Goodall, and Currie have dealt rather with a second injection following a primary sensitization at varying and usually at long intervals, and the reactions they have met with have been of necessity the systemic rather than the local. We have dealt on the other hand with cases given several injections at relatively short intervals (twenty-one days) which approximates the conditions noted by Arthus in his rabbits. It is quite probable that the mechanism of this form of local anaphylactic intoxication differs from the one that underlies the more systemic reactions.

We have as yet obtained no material for histological examination from these human cases. A histological study of Arthus' phenomenon in rabbits has been made by Arthus and Breton[9] and by Thompson and Marchildon.[10]

CONCLUSIONS.

An immediate localized reaction of anaphylaxis in the nature of edema and infiltration with tenderness, followed in untreated cases by necrosis, occurs in human beings on reinjection with antitoxin. The percentage of cases in which this reaction occurs increases directly with the number of injections at short intervals given subsequent to a primary injection. This local reaction corresponds in all particulars to the Arthus' phenomenon in rabbits. The local reaction may or may not be associated with the immediate systemic symptoms described by v. Pirquet and Schick; as the number of repeated injections at short intervals (twenty-one days) is increased, the v. Pirquet and Schick reaction decreases in proportion to an increase in the local reaction. The discovery of this

lesion completes the analogy between the serum sickness in human beings and the phenomena of serum anaphylactic intoxication in animals.

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