

TWO CASES OF ANAPHYLACTIC SERUM DISEASE OVER
SIX YEARS AFTER THE PRIMARY INJECTION
OF HORSE-SERUM (YERSIN'S ANTI-
PEST SERUM)*

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The widespread interest in hypersusceptibility and allergy and their relation to infectious disease leads me to report two cases of this nature following over six years after the primary injection of horse-serum.

I desire also to express the personal feeling that the use of diphtheria antitoxin for the immunization of *contacts* (the immunizing dose) should be avoided as often as practicable. I believe it is much wiser and shows more consideration for the patient for contacts to be examined from day to day and for cultures from the throat to be examined as well. In this way the disagreeable features of serum disease and the indiscriminate and widespread sensitization of many persons to horse-serum will be avoided.

Serum disease is a term used by von Pirquet and Schick¹ to denote the clinical manifestations following the injection of horse-serum. These symptoms may follow the primary, secondary, or other subsequent injection of serum. The first injection of horse-serum often causes symptoms peculiar to the serum itself, such as urticaria, fever, edema and joint pains. These are not due to the antitoxin, but to the horse-serum, and they only occasionally occur immediately after the injection. There is nearly always a latent or incubation period of eight to twelve days. Von Pirquet has noted that following the second injection of horse-serum, the reaction is altered as to time, quantity and quality; and these altered manifestations he has termed allergy (altered reaction).

With regard to the incidence of serum disease, Weaver² records that 31.1 per cent. of 692 patients with diphtheria to whom serum was administered, observed for ten days or more, exhibited the reaction.

The amount of serum injected to a great extent determines the appearance of the reaction. Thus, Weaver notes that when 1 to 9 c.c. of serum was administered, 10.9 per cent. of patients, observed for ten days or more, showed a reaction. When 100 to 109 c.c. were given, 44.4

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1. Von Pirquet and Schick: *Leipsic, Denticke, 1905.*

2. Weaver, G. H.: Serum Disease, *THE ARCHIVES INT. MED.*, 1909, iii, 485.

per cent. of patients showed a reaction; while in eight patients, given 170 to 280 c.c. of serum, all, or 100 per cent., showed a reaction.

Serum disease following a primary injection of horse-serum: This appears after an interval between the injection and the appearance of symptoms. At the end of the period of incubation, the symptoms suddenly appear. Locally, there is redness and itching of the skin. The general symptoms are fever, edema, skin eruptions, such as urticaria and erythema, swelling of lymph-nodes, leukopenia, joint pains, occasionally nausea and vomiting; there is some headache, backache and soreness and aching of the muscles, and in severe cases prostration and a tendency to fainting.

Serum disease following a secondary injection (toxic injection) given after a considerable interval: (Anaphylaxis). Ten days or more after a primary injection the exhibition of a second injection elicits symptoms of serum disease, either immediately or after a period of incubation shorter than that following a primary injection (allergy). The "immediate" reaction occurs within a day; while the "accelerated" reaction occurs usually within five to seven days after the secondary injection. The local symptoms are specific edema and urticaria at the site of inoculation. The general symptoms are fever, chilliness, exanthematous eruptions, urticaria, edema and joint pains, and in severe cases there is prostration and a tendency to fainting.

Von Pirquet³ states that after the first injection of horse-serum, serum disease appears seldom before the sixth day, oftenest on the eighth or ninth day, but frequently later. When individuals receive a secondary injection, the symptoms usually appear as an immediate reaction within twenty-four hours, and he noted that in children receiving a second injection, a number reacted on the sixth and seventh days. This von Pirquet and Schick called the "accelerated" reaction.

The secondary injection must be many times larger in amount than the minimum "sensitizing" injection in order to elicit visible symptoms; so that on this account it would seem to be impossible to determine by means of a cutaneous reaction whether an individual were sensitive to horse-serum.

Von Pirquet explains the phenomena of anaphylaxis or allergy as follows: In serum disease, for example, horse-serum is injected into man, and antibody is formed. We see at this time that symptoms of disease appear and the supposed connection is that the symptoms are due to toxic bodies formed by the digestion of the antigen (allergen) through antibody. On a second injection ("toxic dose") it is assumed (a) that the antibody is already present and when the horse-serum is injected the

3. Von Pirquet: THE ARCHIVES INT. MED., 1911, vii, 259 and 383.

toxic bodies are now formed and elicit an immediate reaction. It is assumed (b) if the second injection follows long after the primary injection the blood is free from antibody as well as horse-serum; but the body cells, however, having once made them, now make antibodies rapidly, so that in this case antibodies are formed more or less quickly. The toxic bodies are then formed and elicit the symptoms in an "accelerated" reaction.

In severe cases of serum disease there is more or less prostration and cardiovascular weakness. These symptoms are no doubt analogous to those elicited in experimental animals on the administration of secondary toxic doses of horse serum to sensitized subjects, and Auer⁴ has called attention to the interesting fact that symptoms and signs of anaphylaxis differ considerably in three species of animals which have so far been carefully studied. The characteristic drop in blood-pressure of dogs shown graphically so well by Pearce and Eisenbrey,⁵ is not found in the acute cases of anaphylaxis in the rabbit and guinea-pig. The large, pale, inflated lungs in the guinea-pig are not found in the dog or rabbit; and, again, the intravital rigor of the heart muscle in the rabbit is not seen in the dog or guinea-pig. In the rabbit Auer demonstrated that the heart itself is the vital cause of death in acute anaphylaxis in rabbits.

CASE REPORTS

Among the personnel at Ancon Hospital in May, 1905, S. T. D., who performed the autopsy, and H. W., an attendant, were exposed to a case of bubonic plague and each received 10 c.c. of Yersin's antipest serum. The same individuals, in October, 1911, were similarly exposed to a case of septicemic plague, and again received 10 c.c. of Yersin's antipest serum. At this time fifteen other individuals who had been exposed received injections of the serum. Among these was H. C. C., and of the seventeen persons injected, S. T. D., H. W. and H. C. C. developed serum disease, while none of the fourteen who had not been previously sensitized by horse-serum developed any symptoms of serum disease.

CASE 1.—S. T. D., physician, aged 39, had never had diphtheria, nor received injections of horse serum. He performed an autopsy on a case of bubonic plague June 23, 1905, and on this date received the equivalent of 10 c.c. of Yersin's antipest serum. This was a dried horse serum taken up with saline solution. No symptoms of serum disease followed the injection.

Oct. 17, 1911, nearly six years and four months later, he performed an autopsy on a case of septicemic plague and the following morning received 10 c.c. of Yersin's antipest serum (liquid horse serum). Following the injection there was some redness at the point of inoculation, but no other signs until October 23 (sixth day), when the skin area corresponding with the location of the injection

4. Auer: *Jour. Exper. Med.*, 1911, xiv, 493.

5. Pearce and Eisenbrey: *Jour. Inf. Dis.*, 1908, vii, 573.

itched intensely and an urticarial rash 6 to 7 cm. in diameter appeared there. The following morning (seventh day) the urticaria spread to the groins, inner aspects of thighs and the scalp. By noon almost all parts of the body above the knees were involved. While the pain and discomfort were severe, there were no other symptoms until 1.30 p. m., when he was awakened from a siesta by a feeling of intense depression as though fainting. The pulse could not be detected at the wrist. Yawning or sighing was frequent. A few minutes later the pulse was found to be 46, the features ashy-white, there was cold perspiration and an intense feeling of prostration. During the afternoon periods of intense stinging or tingling of the skin with tremendous edema of the scalp, lips, forehead and body were followed by attacks of prostration and feeble pulse. Each period lasted about fifteen minutes. There were also small circumscribed patches of pain in the epigastrium, esophagus (?) and right chest below the right nipple. On swallowing a glass of water on one occasion, it appeared that there was some swelling of the mucosa of the esophagus, for there appeared to be some resistance to the passage of fluid. During the afternoon attempts at rising and walking a few steps were quickly followed by fainting sensations and hallucinations of vision. Strychnin sulphate 1/30 gr. was administered hypodermatically in the left arm and the arm remained very tender and sore for two days. The intense itching kept up during the night but there was no distress or prostration. On October 25 there was some urticaria of the legs, particularly the soles of the feet. The patient could not sit up without discomfort. Large urticarial wheals appeared on the neck in the afternoon and there was some general neuralgia-like pain.

October 26: During the night there were large patches of urticaria on the knees and during the day backache and neuralgic pains all over the body. It appeared to the patient that the spells of depression or prostration were to some extent averted if the desire to scratch the areas of urticaria were controlled.

October 27 to 30: Patient felt weak, the muscles were sore and he had a haggard look. November 1: General feeling of well-being returned. November 2: A papular rash that itched or tingled slightly appeared on the breast and sides of chest from the fourth to the eighth ribs. This rash remained for three or four days.

CASE 2.—H. W., negro, native of Grenada, ward attendant. He received an injection of horse serum June 23, 1905. The secondary injection was received Oct. 18, 1911. Erythema at the point of inoculation was noted October 19. On the night of the twenty-sixth urticaria appeared and the patient awoke on the morning of the twenty-seventh at 2 a. m., feeling "stified." He took a drink of water and became covered with sweat. Could not go on duty this morning and remained off duty the twenty-eighth and twenty-ninth. Sticking pains in the chest were felt on the night of the twenty-sixth and twenty-seventh. Fainting sensations were experienced on getting out of bed or on taking an erect position after stooping over. On October 30 he returned to duty and for two or three days felt weak and sore in all his muscles.

H. C. C., who also developed symptoms of serum disease, was exposed to the case of plague of Oct. 17, 1911, and received on October 18, 10 c.c. of Yersin's antipest serum. October 20, local ("specific") urticaria appeared at the site of inoculation. October 26 there was swelling of the arms, face and hands with more urticaria at the point of inoculation, and slight vertigo on rising.

H. C. C. had received horse serum previously; September, 1906, 5 c.c. + — diphtheria antitoxin. September, 1906, 5 c.c. + — diphtheria antitoxin. October, 1906, 15 to 20 c.c. + — diphtheria antitoxin.

Shortly after the October (1906) injection local urticaria of the thigh appeared, and ten days after the injection of serum there was tremendous universal edema, with edema of the throat and larynx, causing some anxiety among his confreres. Between October, 1906, and April, 1907, he received diphtheria antitoxin several times, and on one occasion had a measles-like rash.

In this small series of cases of anaphylactic serum disease, only three of the seventeen individuals receiving serum experienced any symptoms of serum disease, and each one of these three persons had previously been sensitized by injections of horse-serum. S. T. D. and H. W. six years and four months, and H. C. C. five years previously. On this last occasion, H. C. C. had a late "immediate" (?) and an "accelerated" reaction. S. T. D. had an "accelerated" reaction and H. W. had a late "accelerated" reaction.

Considering the fact that the only individuals who suffered from serum disease were those who had been sensitized by previous injections of horse-serum, and on account of the very disagreeable symptoms and consequent loss of time from business, together with the doubtful value of Yersin's serum in preventing or aborting an attack of plague, its indiscriminate use for the immunization of contacts is considered inadvisable.