

SEVERE ALLERGIC REACTION CAUSED BY SILK AS A CONTAMINANT IN TYPHOID-PARATYPHOID VACCINE

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BIZARRE and unexplained reactions, such as purpura, urticaria, vascular collapse, and fatal shock, which follow the parenteral administration of biologic products are not uncommon and have been reported from time to time in the literature.¹⁻⁷ Alexander,⁸ in a review of the subject, states that such reactions to vaccines are "more frequently due to components of the culture media than to the infectious agent itself." Systemic reactions following the administration of typhoid vaccine which were characterized by severe asthma have not been reported in the literature. When other types of systemic reactions have occurred, they have generally followed the intravenous and not the subcutaneous administration of the vaccine.

An instance of a severe asthmatic reaction following the subcutaneous administration of typhoid-paratyphoid vaccine recently came to our attention. The patient (R. B.) was a 13-year-old boy with a past history of bronchial asthma and ragweed hay fever who had been under the care of two of the authors (R. F. and M. W.). He had received the usual immunizing injections against pertussis, tetanus, and diphtheria. In 1952 he had received a series of 3 subcutaneous injections of typhoid vaccine. In 1953 and 1954, booster doses of triple typhoid vaccine were administered uneventfully. In June, 1955, another booster dose of 0.5 ml. of typhoid vaccine was given subcutaneously. Within 10 minutes the patient, who had been free of asthma since March, 1947, began to cough, became dyspneic, and developed a severe attack of bronchial asthma. Epinephrine was administered, with immediate relief.

Several weeks after this incident a sample of the patient's blood was drawn for passive transfer studies. With the patient's serum, cutaneous sites were prepared on normal individuals. For testing purposes, 3 preparations of typhoid vaccine were obtained from pharmaceutical companies, while a fourth one was supplied by a health department laboratory. These various vaccines will be referred to as Brands A, B, C, and D.

One week after preparation, the passive transfer sites were tested with various dilutions of the triple typhoid vaccine (Brand A) which had precipitated the reaction in Patient R. B. Definite positive reactions were obtained with this product. With triple typhoid vaccine from the 3 other sources, no reactions occurred on the passive transfer sites (Table I).

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TABLE I. PASSIVE TRANSFER STUDIES ON SERUM R. B. WITH VARIOUS BRANDS OF TYPHOID VACCINE

RECIPIENT	TEST MATERIAL	DILUTION	RESULTS OF TESTS	
			SENSITIZED SITE	CONTROL SITE
3	Typhoid vacc. A	1:10	++	0
1, 2	Typhoid vacc. B	1:10	0	0
1	Typhoid vacc. B	None	0	0
4	Typhoid vacc. C	1:10	0	0
5	Typhoid vacc. D	1:10	0	0

0 = negative; + = slight positive; ++ = moderate positive; +++ = marked positive; ++++ = very marked positive.

Attempts were then made to identify the offending allergenic factor in vaccine A. Passive transfer tests were carried out with the materials contained in the media in which the organisms had been grown. None of these materials elicited a positive reaction. (Table II.)

TABLE II. PASSIVE TRANSFER STUDIES ON SERUM R. B. WITH CONSTITUENTS OF CULTURE MEDIA USED IN PREPARATION OF TYPHOID VACCINE BRAND A

RECIPIENT	TEST MATERIAL	DILUTION	RESULTS OF TESTS	
			SENSITIZED SITE	CONTROL SITE
3	Beef heart infusion	1:10	0	0
5	Beef	0.05 mg. N/ml.	0	0
3	Tryptic peptone	1:100	0	0
3	Peptic peptone	1:100	0	0

It was now apparent that commercial vaccine A contained an unidentified allergen and that this allergen was not present in the constituents of the media. This allergen was absent from Brands B, C, and D and was capable of eliciting passive transfer reactions on sites prepared with the serum of our patient. At this point, we learned from Company A that filtration through silk, an allergen to which our patient was skin-sensitive, was part of the procedure employed in the preparation of Brand A vaccine. We were also informed by Company A that another patient who had been injected with tetanus toxoid prepared by them had had an allergic reaction which, it was suspected, was due to silk sensitivity.⁹ A positive passive transfer reaction to a test with silkworm extract (0.01 mg. N per milliliter) was then demonstrated at a site sensitized with the serum of Patient R. B. Strong positive reactions were also obtained on tests with a diphtheria toxoid preparation made by Company A. In addition, 1:10 dilutions of extracts of "new" and "old" silk filters used in the

TABLE III. PASSIVE TRANSFER STUDIES ON SERUM R. B. WITH DIPHTHERIA TOXOID AND MISCELLANEOUS MATERIALS USED IN THE PREPARATION OF TYPHOID VACCINE BRAND A

RECIPIENT	TEST MATERIAL	DILUTION	RESULTS OF TESTS	
			SENSITIZED SITE	CONTROL SITE
1	Diphtheria toxoid Brand A	1:100	+ ±	0
5	Extract of used silk filter	1:10	++	0
1	Silkworm extract	0.01 mg. N/ml.	+ + ±	0
6	Extract of new silk filter	1:10	+++	0
2	"Extract" of pink-red rubber plugs	1:10	0	0
3	"Extract" of gray rubber plugs	1:10	0	0

preparation of Brand A typhoid vaccine also gave positive transfer reactions. "Extracts" of the rubber plugs routinely used as a closure for the vials of Brand A typhoid vaccine were negative. (Table III.)

Cross-neutralization studies were then undertaken. (Table IV.) Sites which had been previously tested with silk-filtered typhoid vaccine A failed to react when retested with the same material. Sites which had failed to react to Brands B and C, which contained no silk, reacted strongly when retested

TABLE IV. CROSS-NEUTRALIZATION STUDIES ON SERUM R. B. WITH SILK ANTIGEN AND TYPHOID VACCINES A, B, C, AND D

RECIPIENT	SITE NO.	INITIAL TEST		RETEST		NEUTRALIZATION BY INITIAL TEST
		ANTIGEN	RESULT	ANTIGEN	RESULT	
1,2,3	1	Vacc. A	+++	Vacc. A	0	Complete
1,2	2	Vacc. A	+++	Vacc. B	0	Complete
1,2	3	Vacc. A	+++	Vacc. C	0	Complete
1,2,3	4	Vacc. A	+++	Vacc. D	0	Complete
1/2/3	5	Vacc. A	+++	Silkworm*	0	Complete
1,2	6	Vacc. B	0	Vacc. A	+++	None
1,2	7	Vacc. B	0	Vacc. B	0	
1,2	8	Vacc. B	0	Vacc. C	0	
1,2,3	9	Vacc. B	0	Vacc. D	+++	None
1,2,3	10	Vacc. B	0	Silkworm	+++	None
1,2,3	11	Vacc. C	0	Vacc. A	+++	None
1,2	12	Vacc. C	0	Vacc. B	0	
1,2	13	Vacc. C	0	Vacc. C	0	
1,2	14	Vacc. C	0	Vacc. D	+++	None
1,2	15	Vacc. C	0	Silkworm	++	None
1,2,3	16	Vacc. D	+++	Vacc. A	0	Complete
1,2,3	17	Vacc. D	+++	Vacc. B	0	Complete
1,2,3	18	Vacc. D	+++	Vacc. C	0	Complete
1,2,3	19	Vacc. D	+++	Vacc. D	0	Complete
1,2,3	20	Vacc. D	+++	Silkworm	0	Complete
1,2,3	21	Silkworm	++	Vacc. A	+	Incomplete
1,2,3	22	Silkworm	++±	Vacc. B	0	
1,2,3	23	Silkworm	+++	Vacc. C	0	
1,2,3	24	Silkworm	+++	Vacc. D	+	Incomplete
1,2,3	25	Silkworm	++±	Silkworm	0±	Almost complete

*Silkworm antigen solution contained 0.01 mg. N per milliliter. Sites prepared with 0.1 ml. of serum R. B. and tested after 7 days. Intracutaneous tests made with 0.02 ml. of antigen extract. Silkworm extract prepared by Allergy Laboratory of Jewish Hospital, Brooklyn, N. Y.

with Brand A. In the same manner, when sites tested with B and C were retested with silk, positive reactions were elicited. When Brand D, which had originally given negative reactions (Table I), was used in the cross-neutralization studies, we were surprised to find that it now gave a strongly positive reaction and neutralized all of the silk reagins in the serum. The vial used in the neutralization study was not the same one used for the tests recorded in Table I. From correspondence with the manufacturer of Brand D, we learned that silk is occasionally used in their filtering procedures. The positive reaction to Brand D is in accord with the findings of Coleman¹⁰ who encountered a case similar to our own and who, on the basis of our experience, was able to demonstrate that silk was the offender in his patient.

The neutralization studies demonstrated that the silk reagins in serum R. B. had been exhausted by the reactions to Brands A and D typhoid vaccine, but had not been affected by Brands B and C. It was apparent from these studies that substantial amounts of silk antigen are present in vaccines when silk is used for the filtering process.

Neutralization studies could not be continued to determine why the initial tests with silkworm (Table IV) failed to neutralize the sensitized sites to subsequent tests with vaccines A and D. This might have been based on quantitative factors with vaccines A and D containing more antigen than the silk extract (0.01 mg. N per milliliter). It is to be noted that the 0.01 dilution of silkworm extract did not on the initial test completely neutralize a site to this antigen (Table IV, site 25). There is also the possibility that a qualitative factor was involved and that the silkworm antigens in the extract and in the vaccines A and D were not completely identical. Since the antigenic materials needed to carry on such studies were not readily available and the outcome of these studies had no direct bearing on the general conclusions which were to be drawn, no effort was made to pursue them further.

Silkworm allergen was undoubtedly the agent which caused the constitutional reaction suffered by our patient following the injection of typhoid vaccine. We have learned that although nylon is used routinely in the filtering process by many pharmaceutical houses, a situation occasionally arises when it becomes necessary to substitute silk for nylon. The presence of this hidden antigen in some biologicals may have serious consequences since silk sensitivity is common among allergic patients. If the use of silk as a filter cannot be avoided, the presence of silk antigen in a biological product would seem to warrant a warning by the manufacturer on each package advising caution in the administration of the product to silk-sensitive individuals. The unsuspected presence of this antigen should also be made known to immunologists and clinicians who may use these materials experimentally and may obtain unexplained immunologic responses as a result of the presence of the hidden silk antigen.

SUMMARY

Reactions to silk extract and to certain biologicals which had been filtered through silk were demonstrated in the serum of a patient who had experienced a severe asthmatic attack shortly after receiving a subcutaneous injection of triple typhoid vaccine. Cross-neutralization tests showed that silk-filtered vaccines exhausted all the silk antibodies in the patient's serum, whereas those vaccines not silk-filtered did not affect the reactivity of the serum.

The silk antigen in biological products is a potential hazard to any silk-sensitive individual. The presence of this antigen in any parenterally administered biological should be properly indicated and a warning of its potential danger to silk-sensitive individuals should be included in the instructions for administration.

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