

Allergic reactions due to plague vaccine

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Twenty-two patients had allergic-type reactions, primarily immediate urticaria, following plague vaccine immunization. The contralateral upper arm was involved with striking frequency. None of the reactions was serious, and all responded readily to symptomatic therapy. A reaginic pathogenesis for these reactions could be implicated in only about half of the patients. The precise antigen was not identified, but the plague bacillus or its products, rather than trace substances in the vaccine, was suspected.

Bubonic plague still remains an important potential medical problem in Southeast Asia. Active immunity can be effectively induced with the administration of a formalin-killed bacterial vaccine. All members of the United States Armed Forces are immunized early in the course of active duty, and, if necessitated by geographical assignment, booster injections are given at periodic intervals to maintain adequate antibody levels.

In 1968, a report by the Advisory Committee on Immunization Practices of the United States Public Health Service¹ noted only mild adverse effects from the plague vaccine. These were of the irritative or toxic variety. Allergic-like symptoms were not mentioned. The manufacturer's brochure* describing the plague vaccine notes about a 10 per cent incidence of reactions such as "generalized malaise, headaches, local erythema and induration, and mild lymphadenopathy, and hyperpyrexia." It also states that a few cases of sensitivity reactions manifested by urticarial and asthmatic phenomena have been reported. Military physicians involved with mass immunizations have been aware that plague vaccine is probably one of the most common causes of significant adverse reactions.

Over an 18 month period, 22 patients with allergic-type reactions following plague vaccine were seen in the Allergy Clinic, Brooke General Hospital,

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Fort Sam Houston, Texas. Almost all had urticaria as the major clinical feature. Since such reactions have not been widely reported and do present some unique features, they serve as the basis for this communication.

CLINICAL DATA

Immunization procedure

Plague vaccine contains 2,000 million formaldehyde-killed plague bacilli per milliliter of sodium chloride solution. Other ingredients are 0.04 per cent formalin, 0.5 per cent phenol, and trace amounts of beef heart extract, yeast extract, agar, peptones, and peptides of soya and casein.

According to present military procedure, primary immunization consists of 1.0 ml. of plague vaccine given as an initial dose followed 3 months later by 0.2 ml. Further booster doses of 0.2 ml. are given at 6 month intervals to those military personnel assigned to Southeast Asia and exposed to the possibility of plague infection. At Fort Sam Houston, immunizations are most frequently given at a dispensary. Patients with suspected adverse allergic-type reactions are usually referred to the Allergy Clinic for evaluation.

During this 18 month period in which 22 patients with allergic reactions were seen, the total number of plague immunizations administered could not be estimated reliably. Approximately one thousand 20 ml. bottles of vaccine were supplied to the dispensaries during this period. However, all the vaccine may not have been used, and the material was used for both initial 1.0 ml. and



Fig. 1

Urticaria involving the contralateral arm only, occurring 15 minutes after plague vaccine injection.

Table I. *Summary of clinical data*

<i>Reactions</i>	<i>Patient</i>	<i>Atopy</i>	<i>No. plague injection</i>	<i>Skin test* (1:100 vaccine)</i>	<i>Concomitant immunizations</i>
Generalized urticaria†	W. H.	+	1	3+	Typhus and tetanus
	M. S.	+	1	Negative	
	T. T.		1	2+	Smallpox
	B. C.		1	Negative	
	M. N.	+	1	1+	Cholera
	G. P.		1	Negative	Cholera, tetanus, and yellow fever‡
	A. A.		1	Negative	Typhus
Bilateral upper arm urticaria	E. F.		1	2+ (1:1,000)	
	P. S.		1	Negative	Influenza
	D. B.		1	Negative	Smallpox
	J. T.	+	1	4+ (1:1,000)	Smallpox
	W. L.		1	2+	Yellow fever, small- pox, and typhus‡
	A. B.		2	Negative	Cholera
	R. W.		2	Not done	Smallpox
Contralateral urticaria	R. B.	+	2	2+ (1:1,000)	
	M. C.	+	1	1+	Smallpox
	H. M.		1	2+ (1:1,000)	Influenza
	D. K.		1	Negative	Smallpox and cholera
Local urticaria	B. B.	+	1	Negative	
	R. M.		1	Negative	Smallpox
Local swelling	M. W.		2	Negative (Pos. delayed)	
Anaphylactic	R. K.	+	1	1+ (Pos. delayed)	Cholera

*Immediate intracutaneous skin test reaction graded on a 1 to 4+ basis.

†Defined as urticaria involving at least 3 separate areas of the body.

‡Subsequent administration of plague vaccine alone described in text.

subsequent 0.2 ml. doses. It is also reasonable to assume that not all adverse reactions were referred to the Allergy Clinic. Thus, the actual incidence of allergic-type reactions from plague vaccine can only be said to be very low.

Personal factors

The 22 patients ranged in age from 18 to 33. There were 19 men and 3 women. Eight patients had an atopic background, and 14 had had no allergic history. Eighteen patients reacted to their first injection of plague vaccine. Of the remaining 4, one had had a similar urticarial reaction following her first plague immunization, and one patient may have had a large local reaction following his first exposure.

Nature of reaction

Immediate urticaria, present within 15 to 30 minutes following plague vaccine, was the major clinical manifestation of these reactions occurring in all but 2 patients. There was a peculiar predilection for the contralateral upper arm. Seven patients had urticaria of a generalized variety, as defined by urticaria involving at least 3 or 4 separate areas of the body. Seven patients had bilateral

Table II. *Summary of immediate skin test reactions*

<i>Reactions</i>	<i>Skin tests</i>	
	<i>Positive</i>	<i>Negative</i>
Generalized urticaria	3	4
Bilateral upper arm urticaria*	3	3
Contralateral upper arm urticaria	3	1
Localized urticaria		2
Local swelling		1 (Pos. delayed)
Anaphylactic	1 (Pos. delayed)	

*One person in this group was not tested.

upper arm urticaria, and 4 patients developed urticaria only over the contralateral upper arm with no lesions about the actual injection site (Fig. 1). Two patients had urticaria only over the upper arm about the injection site. One patient had an anaphylactic-type reaction consisting of tachycardia, chest tightness, and hypotension. This started about 30 minutes after the injection, and some symptoms lasted for 36 hours. The final patient had a large local reaction at the injection site, without evident urticaria. These latter 2 patients both had positive skin tests.

Many of the patients received other immunizations at the same time as the plague vaccine. The history, subsequent administration of vaccine, skin tests, and eventually the typical clinical pattern led to the diagnosis of plague vaccine as the etiological agent. On several occasions, particularly during the early experience, diagnostic immunizations were administered. The following 2 case histories are illustrative:

Patient G. P. developed generalized urticaria 10 minutes after receiving yellow fever, tetanus, plague, and cholera immunizations. He had received tetanus and influenza vaccine previously with no difficulty. Intradermal skin tests with all vaccines were essentially negative. He was then given cholera and yellow fever vaccines on successive days with no difficulty. Subsequently, within 15 minutes following the administration of 0.2 ml. of plague vaccine, he developed urticaria and pruritus over the scalp, inguinal area, and contralateral upper arm. This was readily relieved with epinephrine.

Patient W. L. had bilateral upper arm urticaria shortly after yellow fever, typhus, smallpox, and plague immunization. Skin tests revealed a mild reaction to plague, but at this time its significance was not clear. Yellow fever and typhus were administered with no difficulty. Bilateral urticaria of a milder nature again occurred 15 minutes after 0.2 ml. of plague vaccine.

The urticarial reactions responded quite quickly to epinephrine and antihistamine therapy. There were no serious reactions in this group, and no involvement of the upper respiratory tract was noted. Several patients did not receive medical therapy, and symptoms subsided spontaneously within 1 to 2 hours.

The pertinent clinical data are summarized in Table I.

Skin tests

Preliminary intradermal skin tests with the use of 0.02 ml. of vaccine, performed on 50 control patients, indicated that positive immediate reactions considered nonspecific were usually caused by undiluted vaccine and frequently caused by 1:10 diluted plague vaccine. No reactions were found with a 1:100

Table III. *Results of passive transfer studies*

<i>Patient</i>	<i>Clinical urticarial reaction</i>	<i>Immediate skin test</i>	<i>Passive transfer test</i>
J. T.	Bilateral upper arm	4+ (1:1,000)	4+ (titer 1:30)
M. N.	Generalized	1+ (1:100)	Negative
T. T.	Generalized	2+ (1:100)	2+
R. W.	Bilateral upper arm	Not done	Negative
B. C.	Generalized	Negative	Negative
M. S.	Generalized	Negative	Negative

dilution of plague vaccine, and thus this dilution was the greatest concentration used to indicate significant sensitivity. The majority of the control patients were atopic and of the same age range as the patients under study.

Patients were tested intradermally with 0.02 ml. of 1:1,000 and 1:100 plague vaccines. Tests were read in 15 minutes (1+ to 4+ basis). Patients were advised to report any delayed reactions. The skin test data are summarized in Tables I and II. Eleven patients had negative immediate skin test reactions and 10 had positive tests.* Of these 10 patients, 4 reacted strongly to a 1:1,000 dilution of plague vaccine. The groups of patients with generalized urticaria and bilateral upper arm urticaria were both almost equally divided between positive and negative reactors. Three of the 4 patients with contralateral arm urticaria had positive tests. The 2 patients with urticaria localized about the injection site had negative immediate tests, as did the patient with large local swelling. This latter patient had a typical delayed reaction at the testing site. The patient with anaphylactic type symptoms lasting almost 36 hours had both immediate and delayed reactions.

Passive transfer tests

After proper sterility studies, 0.1 ml. of sera from 6 patients was injected intradermally into 2 nonallergic recipients. Twenty-four hours later each site was challenged with 0.02 ml. of plague vaccine diluted 1:10 in normal saline. Control direct tests with this plague vaccine concentration were negative. The passive transfer reactions were read in 20 minutes, and the results are summarized in Table III.

Sera from 4 patients failed to react. Two of these patients had negative immediate skin reactions, one had a weakly positive test, and direct testing was not done on the fourth patient. Positive passive transfer reactions were elicited with the sera of Patients T. T. and J. T. The intensity of these reactions was similar to each patient's direct intradermal reaction. Further studies with the use of serial threefold dilutions of the serum of Patient J. T. showed the reaction end point titer was the 1:30 serum dilution. Following heating of this serum at 56° C. for 4 hours, the passive transfer reaction was abolished.

Identification of antigen

The precise culture media ingredients on which the plague bacilli are grown could not be obtained from the manufacturer. Therefore, 2 other common

*One patient was not tested.

bacteriological media which contain the trace substances in the plague vaccine were utilized for testing. These were Todd-Hewitt broth* and peptone phosphate broth.† Both were made up in the recommended concentration of 30 Gm. per liter of distilled water. Preliminary skin tests indicated irritative reactions from undiluted and 1:10 diluted broth. Thus, tests were done with 1:100 dilutions of both media.

Direct intradermal skin tests were done on Patient J. T., who had been the most sensitive reactor to plague vaccine. Tests with both broth media were negative. Passive transfer studies were done with sera from Patients J. T. and T. T. Again no reactions were noted following challenge with both media.

Ten milliliters of plague vaccine were centrifuged, leaving a pellet at the bottom of the tube with a clear supernatant. The pellet was washed 3 times and resuspended in 10 ml. of normal saline. Direct skin tests on Patient J. T. were strongly positive with a 1:1,000 dilution of both the resuspended pellet and the supernatant. These reactions were of equal intensity as that induced by whole vaccine. Similar results were obtained in passive transfer tests with sera from J. T. and T. T.

DISCUSSION

Precise data relative to the actual incidence of adverse reactions to plague vaccine were not available. In view of the large number of doses administered and even allowing for some reactions not reported or treated elsewhere, it would appear that reaction incidence is quite low. However, the manufacturer's brochure and personal communication with physicians who have had experience with plague vaccine administered in Vietnam suggest that toxic type reactions are even more common following subsequent booster doses. Whether this increased reaction rate also applies to urticaria or other allergic-type symptomatology is not clear.

The pathogenesis of the urticarial reactions is probably the most important question raised by these observations. Two different mechanisms may be involved. The high incidence of reactions following first exposure to plague vaccine and the frequency of negative immediate skin tests suggest that the reaction is not always mediated through an antigen-antibody reaction. At present the mechanism for this type of probable histamine release and urticaria is unknown. A wide spectrum of drugs and chemicals has histamine release properties unrelated to an immunological pathogenesis.²

Half the patients studied did have immediate skin test reactions. Sera from two of these patients were capable of passively sensitizing the skin of normal human recipients. Loss of this passive transfer reaction capability of the most potent serum following heat inactivation further suggests that reaginic antibody was present and probably mediated some of these allergic reactions. As most pa-

*Todd-Hewitt broth, Difco Laboratories, Detroit, Mich.; beef heart, 500 Gm.; neopeptone, 20 Gm.; bacto-dextrose, 2 Gm.; NaCl, 2 Gm.; disodium phosphate, 0.4 Gm.; sodium carbonate, 2.5 Gm.

†Peptone phosphate broth, Difco Laboratories, Detroit, Mich.; pancreatic digest of casein, 17 Gm.; soy peptone, 3 Gm.; bacto-dextrose, 2.5 Gm.; NaCl 5.0 Gm.; dipotassium phosphate 2.5 Gm.

tients who reacted had never had plague vaccine previously, the initial stimulus for production of this reagin was probably a cross-reacting antigen.

The finding of clinically similar plague vaccine reactions with both positive and negative direct skin tests bears striking resemblance to the pattern long noted in stinging insect-hypersensitive individuals. The pathogenesis of reactions may well be similar.

The ingredient in the vaccine responsible for reactions is most probably the plague bacillus or its products. The nature of the other materials in the vaccine makes their role highly unlikely. There is nothing in the clinical data or in the results of testing with bacteriologic culture media which implicates these trace substances.

The simple experiment of centrifuging the vaccine in an attempt to separate bacteria from other culture ingredients failed to isolate the allergenic component. Several explanations seem possible. It is most probable that bacterial products are present in the supernatant. Alternatively, culture media ingredients could have been sedimented with bacteria into the pellet. Further immunochemical and biological analyses, beyond the scope of this paper, would be required to pursue this aspect of investigation. As at least two mechanisms of pathogenesis have been postulated, it is also possible that several different substances or antigens may be involved.

The strange predilection for urticaria to occur on the contralateral arm is most unusual and, as far as can be ascertained, seems unprecedented. The possible role of an unrelated vaccine injected into the opposite arm contributing to local tissue susceptibility or sensitivity was considered. However, this seemed unlikely as contralateral arm urticaria did occur on several occasions when plague vaccine alone was administered.

Fortunately the urticarial reactions have not been severe, have not involved the upper respiratory tract as commonly occurs in human anaphylaxis,³ and have responded readily to therapy. Furthermore, the reaction was quite self-limited in a number of patients who did not receive any specific treatment. Whether these reactions would be inhibited by prior administration of epinephrine or antihistamines was not determined, but certainly this is a reasonable possibility.

Following the diagnosis of an allergic reaction due to plague vaccine, no further plague vaccine administration was recommended. Present army regulations do not make any geographical assignment limitations in these situations. Therefore, in certain instances one might wish to weigh reaction risks with the risk of contracting plague.

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