Active rabies immunization in an individual hypersensitive to duck embryo vaccine

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Active immunization against rabies was achieved by cautious administration of duck embryo vaccine (DEV) to a child who had skin-sensitizing antibody to the vaccine. Dermal hypersensitivity to DEV was found in 20 per cent of "atopic" individuals, including 60 per cent of individuals with dermal hypersensitivity to chicken eggs. Fatal anaphylactic reactions have not been reported, and immediate hypersensitivity and neurologic reactions rarely occur after immunization with DEV. Since there is greater risk of neurologic reactions to vaccines made from nervous tissue, DEV should be considered when active rabies immunization is indicated, even in the DEV-hypersensitive individual.

Human beings may be actively immunized against rabies by injection of a vaccine made from dried, killed virus grown in duck embryos (DEV)[1-3] or with phenol-killed virus grown in rabbit brain tissue (Semple vaccine).[3] Both vaccines produce a high incidence of local reactions which usually do not preclude completion of the immunization.[1, 3] Neurologic reactions including encephalitis[4] and myelitis[5-6] have occurred after DEV immunization, but their incidence (4 cases in 90,000 treatment series reported to the manufacturer[7]) is much lower than that of 1 in 600[8] to 1 in 8,000[9] courses of immunization with vaccines of nervous tissue origin. For this reason, DEV has been preferred for active immunization. Three cases of anaphylactic shock after DEV immunization have been reported to the manufacturer,[7] and several other instances of probable reactions of immediate hypersensitivity are recorded.[10-13] Although the risk of serious immediate hypersensitivity to DEV in individuals who are allergic to vaccine has not been established, Loofbourow and co-workers[13] reported no difference in reactions to prophylactic DEV treatment among the Peace Corps volunteers with and without histories of allergy, including sensitivity to eggs or chickens. The total apparent risks of immediate hypersensitivity and neurologic allergic reactions would still seem to favor DEV immunizations even in individuals allergic to the vaccine. The successful immunization of such an individual and an estimate of the population at risk for immediate hypersensitivity allergic reactions to DEV are reported.

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TABLE I. Wheal responses to DEV

DEV			15 min. Wheal reaction*									
Concentration (v/v)	Dose (ml.)	Route	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
1:100	0.02	ID	++									
1:10	0.02	ID	+++	++	++	++	+	+	+	+	++	+++
1:10	0.04	SC arm	0									
1:10	0.08	SC arm	0									
1:10	0.15	SC arm	0	0	0	0	0	0	0	+	0	0
1:10	0.30	SC arm	+									
Undiluted	0.025	SC ABD	+	0								
Undiluted	0.05	SC ABD	++									
Undiluted	0.10	SC ABD	++	+								
Undiluted	0.20	SC ABD	++	+	0	0	0	0	0	0	0	0
Undiluted	0.40	SC ABD		+								
Undiluted	0.80	SC ABD			0	0	0	0	0	0	0	0

ID = intradermal; SC = subcutaneous; ABD = abdomen.
*See text.

CASE REPORT

M. K. (SCRF No. 69-1671), a 6-year-old schoolboy who had had mild eczema, rhinitis, and asthma since age 2, had no history of egg intolerance or of adverse reactions to immunizations including measles vaccine at the time of his evaluation at age 4 in May, 1969. He was found to have skin-sensitizing antibody by passive serum transfer (P-K) testing to extract of whole chicken egg. As his mild respiratory and cutaneous symptoms were not aggravated by ingestion of eggs, they had not been eliminated from the diet. In September, 1971, while at a wilderness campsite, he was scratched on the finger by the teeth of an unknown, aggressive dog. He was taken to a hospital where the wound was cleansed and tetanus toxoid given. While the patient was at the hospital, the dog and its owners left the campsite; attempts to find the dog over the next 3 days were unsuccessful. According to the criteria of the World Health Organization,[14] active immunization for rabies was indicated for the child who had suffered a mild exposure to an unknown but potentially rabid animal.

Direct intradermal tests with 0.02 ml. of saline and rabies vaccine (duck embroyo)* at 1:10,000 and 1:1,000 volume to volume (v/v) saline dilutions yielded no wheal reaction greater than 3 mm. in diameter at 15 minutes. Tests with a 1:1,000 v/v dilution of DEV produced a 7 × 8 mm. wheal (++ reaction) at 15 minutes and with a 1:10 v/v dilution of DEV a 12 × 14 mm. wheal (+++ reaction). Despite the presence of skin-sensitizing antibody presumably to avian antigens in the vaccine, it was elected to continue the immunization. Wheal responses to DEV skin tests and immunizing doses are shown in Table I. On the first day of immunization, two-fold increments of the dose which had produced a positive skin test were given subcutaneously in the arm at 20 minute intervals without appreciable wheal reaction. Thereafter, undiluted DEV was administered subcutaneously in the abdomen, the usual site of the administration; wheals equivalent to those of the ++ reaction did occur as the volume of undiluted vaccine was increased. Over the next 10 days the patient continued to demonstrate wheal reactivity on intradermal testing with a 1:10 dilution of the vaccine. By the third day it was possible to give 0.2 ml. and 0.8 ml. DEV injections in the abdomen without reaction. There were no systemic symptoms, nor did delayed reactions occur.

*Eli Lilly & Co., Indianapolis, Ind.

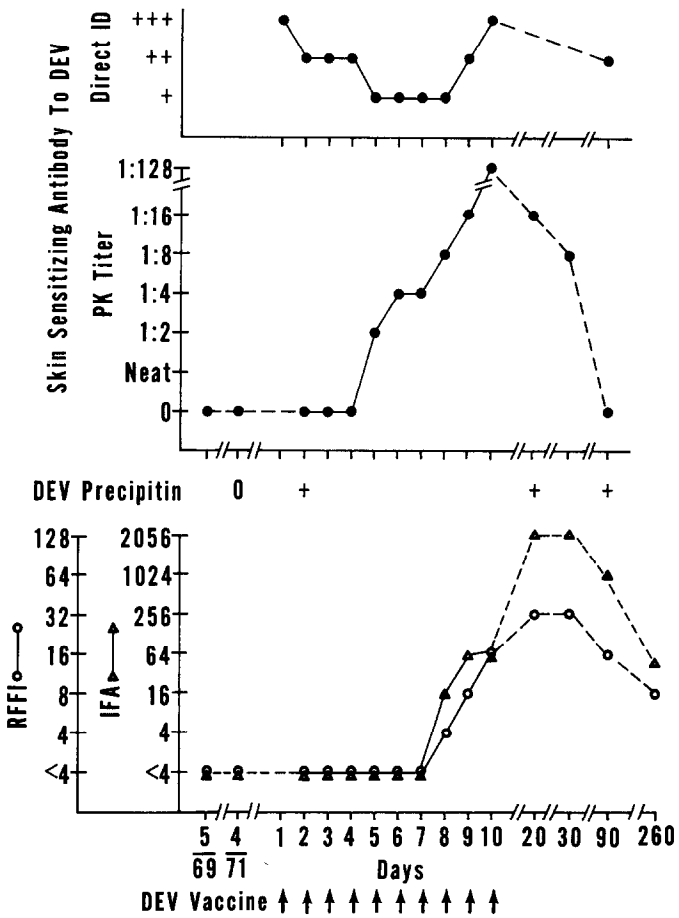


FIG. 1. Whealing to intradermal DEV transiently diminished while serum skin-sensitizing antibodies (P-K titer) appeared during DEV immunizations **(arrows)**. DEV precipitins were noted on the second day and remained present after immunizations. Rabies-neutralizing antibodies detected by fluorescent focus inhibition **(RFFI)** and rabies-specific antibodies measured by indirect fluorescent antibody **(IFA)** appeared by the eighth day of immunization and remained detectable 260 days after initiation of immunization.

Immune reactions to DEV and rabies virus are shown in Fig. 1. Direct skin reactivity was graded from measurements of perpendicular diameters of wheal responses 15 minutes after the injection of 0.02 ml. of 1:10 v/v of DEV intradermally: 0 = less than 5 × 5 mm., + = 5 × 5 to 7 × 7 mm., ++ = 7 × 8 to 10 × 10 mm., +++ = greater than 10 × 10 mm., and ++++ = greater than 10 × 10 mm. with pseudopods. Reaginic antibody was measured by transfer of serial dilutions of serum (aseptically drawn tests for VDRL, Australian antigen, and antibody and microbial growth were negative) to the skin of a nonallergic ("nonatopic," see below) individual previously immunized to rabies followed in 48 hours by challenge of the sites with 0.02 ml of 1:10 v/v DEV. The greatest dilution allowing a ++ wheal at 15 minutes was recorded as the titer end point. Heating the serum at 56° C. for 4 hours removed skin-sensitizing reactivity to DEV. Double immunodiffusion in 0.4 per cent Agarose gel of undiluted patient serum against DEV produced a precipitin line by the second day of immunization. No precipitins to Semple type rabies vaccine* were detected. Specific anti-

*The National Drug Company, Philadelphia, Pa.

TABLE II. Prevalence of dermal sensitivity to DEV

Individuals tested	Wheal-flare reactivity to DEV				
	Negative (1:10 v/v)	Positive			
		1:10 v/v	1:100 v/v	1:1,000 v/v	1:10,000 v/v
33 "nonatopic"	32 (97%)	0	1	0	0
67 "Atopic"	54 (81%)	6	2	4	1
57 Egg(-)*	50 (88%)	5	2	0	0
10 Egg(+)†	4 (40%)	1	0	4	1

*Less than ++ 15 minute wheal reaction to 1:500 w/v extract of whole chicken egg.
†++ or greater reaction to 1:500 w/v extract of whole chicken egg.

bodies to the rabies virus were measured by an indirect antibody (IFA) staining procedure and a neutralizing antibody titration procedure based on the specific inhibition of fluorescent rabies plaques in tissue cultures (rabies fluorescent focus inhibition [RFFI] test).[15]

The boy tolerated the testing and immunization procedures without ill effect throughout the period of observation. Booster immunizations were not given beyond 10 days as antibodies developed promptly and were subsequently shown to persist beyond the usual incubation period for rabies in human beings.

PREVALENCE OF IMMEDIATE SKIN SENSITIVITY TO DEV

Results of skin tests for wheal reactivity to 0.02 ml. of various dilutions of DEV in 100 patients seen in the Allergy and Immunology Division at Scripps Clinic and Research Foundation are listed in Table II. Patients were considered "nonatopic" if they demonstrated no ++ wheal reaction on skin testing with aqueous extracts of common allergens including house dust, animal danders, mold spores, pollens, and chicken eggs. In 33 such individuals only one had a ++ wheal response to 1:10 v/v dilution of DEV; DEV (a 10 per cent suspension of duck embryo) provoked a + or ++ wheal reaction in all individuals tested. Of 67 patients with ++ wheal reactivity to at least one antigen ("atopics"), 54 (81 per cent) had no evidence of skin-sensitizing antibody to DEV. Thirteen patients did have positive DEV reactions, the majority at relatively high concentrations of the vaccine. Fifty-seven of these "atopic" individuals had negative skin tests to eggs; 7 of these demonstrated wheal reactivity to DEV at high concentrations. The highest incidence and degree of wheal reactivity occurred among the 10 atopic individuals who reacted positively to chicken eggs. Four of these individuals had positive reactions at a 1:1,000 dilution of DEV and one at a 1:10,000 dilution. The case reported would have fallen into the category of subjects who were positively reactive to eggs and to DEV diluted 1:100.

COMMENTS

Evidence obtained by either medical history or wheal and flare skin reactivity of an individual's potential for immediate hypersensitivity reactions to a biological or chemical agent is a strong warning to proceed with caution in the therapeutic use of such an agent. Instances of fatal anaphylaxis after administration of horse serum, penicillin, and hyposensitization injections are examples to support such caution. Still, not all individuals who have immediate hypersensitivity manifest disease on exposure to antigens to which they show

wheal and flare reactivity in the skin. For example, at least 5 per cent of asymptomatic individuals have skin-sensitizing antibodies to common inhalant allergens,[16] and 40 per cent of diabetic patients treated with insulin[17] have reaginic antibodies to insulin.

The risk of fatal rabies infection needs be weighed against the risk of adverse reactions to immunization (with or without passive immunization) with the vaccines available. These risks have been considered by the World Health Organization in their recommendations for preventive treatment of rabies.[14] The results (Table II) of skin testing with DEV reported in this series suggest that almost 20 per cent of all "atopic" individuals and 60 per cent of those who have positive skin reactions to chicken eggs might respond with immediate hypersensitivities to DEV. That no instances of fatal anaphylactic reactions and only a few instances of immediate hypersensitivity reactions have been reported[7, 10-13] among the estimated 30,000 courses of DEV treatment given each year in the United States[18] suggests that potential immediate hypersensitivities to treatment with DEV are relatively unimportant. It is conceivable and even likely that patients, such as the one reported here, have or quickly develop serum antibodies to DEV which "block" immediate hypersensitivity reactions that would be produced by the reaginic antibody.

The incidence of neurologic reactions[8-9] is appreciably higher with vaccines derived from nervous tissue (Semple vaccine) than with DEV. Purified rabies vaccines relatively devoid of the tissue antigens which are presumed to be the cause of immediate hypersensitivity and neurologic allergic reactions have been developed[19-20] but are not yet available in the United States. Thus DEV should currently be considered the vaccine of choice for active immunization against rabies even in individuals hypersensitive to DEV, providing appropriate precautions, such as those reported here, are observed.

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