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ALLERGENIC AND ANAPHYLACTOGENIC PROPERTIES OF VACCINES PREPARED FROM EMBRYONIC TISSUES OF DEVELOPING CHICKS¹

I. SKIN-SENSITIVITY FOLLOWING THE SUBCUTANEOUS INOCULATION OF TYPHUS-VACCINES IN MAN

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Viral and rickettsial vaccines prepared from cultures grown in embryonic chick tissues are being used with increasing frequency. Yellow-fever and equine encephalomyelitic vaccines are prepared from infected chick-embryos, typhus- and spotted-fever vaccines from yolk-sacs, and influenzal vaccine from allantoic fluid. Vaccines against yellow fever, typhus, and influenza are being extensively used to immunize military personnel, and equine encephalomyelitic vaccine is used routinely to immunize horses and mules in the Army.

In view of the extensive use of egg-vaccines in the Army the following study was begun in 1942 in order to obtain information on the possible allergenic and anaphylactogenic properties of these materials.

The possibility that vaccines prepared from fertile eggs might sensitize man to the egg-proteins has already been examined by a number of investigators. The effects of the use of an equine encephalomyelitic vaccine were investigated by Beard, Finkelstein, and Beard (1). These workers observed little reaction in individuals receiving the primary inoculation, yet a group of persons receiving a second course of injections showed a definite general reaction. The data presented by Graham (2), Schoening (3), Wolfe and Trum (4) show clearly the danger of anaphylactic phenomena and even death following the administration of an equine encephalomyelitic vaccine in animals.

Van der Scheer, Wyckoff, and Bohnel (5) have shown that guinea pigs can be sensitized with an equine encephalomyelitic vaccine and subsequently a fatal anaphylactic shock can be induced by a second inoculation of vaccine. On the other hand, Cox (6) failed to sensitize guinea pigs or induce an anaphylactic reaction after injections of 0.1 to 1.0 ml. of a typhus- or Rocky Mountain spotted-fever vaccine. It should be observed that the original typhus- and Rocky Mountain spotted-fever vaccine employed by Cox consisted of a washed suspension of rickettsiae which is different from the vaccines now in use. Finally, Berge and Hargett (7) working with yellow-fever vaccine and crude extracts of normal chick-embryos, concluded that chick-embryo proteins derived from embryos of different ages possess the power to produce anaphylactic sensitization in guinea pigs in direct ratio to the

¹ Joint investigation initiated by the Division of Viral and Rickettsial Diseases, Army Medical School. The original report was made to the Surgeon General on 19 January 1944. The publications in the present form were condensed from the original report, certain additions being made to bring the subject up to date.

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age of the embryo employed. Chick-embryo extract from 10-day or younger embryos was found to be weakly anaphylactogenic while that from 14-day embryos was highly so.

During and since the preparation of this report, anaphylactic reactions following the use of egg-vaccines in man have been reported. Swartz (8) reported a reaction which occurred five minutes after an injection of cholera- and yellow-fever vaccines, when the patient became cyanotic, breathing was difficult and he lost consciousness. After several injections of adrenalin improvement was noted. Subsequent skin-tests, confirmed by passive-transfer tests with serum, showed positive reactions to egg-white, chicken-meat and yellow-fever vaccine and no reaction to cholera-vaccine. Roth (9) reported nine cases developing reactions following the inoculation of typhus-vaccine. Four of these, who gave a history of allergy to egg, developed severe reactions. One patient had dyspnea, cough, weakness, and sub-sternal pressure following the first inoculation of typhus-vaccine. On examination he was cyanotic and covered with an urticarial eruption. Some time later he received 0.1 ml of typhus-vaccine and again developed an asthmatic attack. Sprague and Barnard (10) reported two instances of severe reactions in egg-sensitive individuals following the inoculation of yellow-fever or typhus-vaccines. One case was reported (11) in a child who promptly died of an anaphylactic reaction following the inoculation of a spotted-fever vaccine. A soldier who had received cholera- and typhus-vaccines almost immediately had difficulty in breathing, became cyanotic and died in about 30 minutes following inoculation. The necropsy-findings were typical of an anaphylactic death. A review of the history revealed the existence of egg-sensitivity since childhood. A severe reaction occurred in a WAC following the first injection of typhus-vaccine. Because a subsequent skin-test produced a severe reaction, immunization was discontinued. Her serum, in passive-transfer tests, reacted to typhus-vaccine.³ A soldier who received influenzal vaccine developed a severe anaphylactic reaction with respiratory and cardiac failure and died two hours after inoculation. There was a history of asthma since childhood.⁴

Rubin (12) reported a severe reaction in a soldier with angioneurotic edema, difficulty in breathing, and pain in the chest following immunization with typhus- and yellow-fever vaccines. The patient reacted by direct skin-tests, and his serum in passive-transfer tests reacted to yellow-fever and typhus-vaccines.

The possibility that the administration of chick-embryo vaccines to egg-sensitive individuals might be hazardous was recognized.⁵ This has been borne out by subsequent accidents. While these severe reactions can occur in egg-sensitive individuals it should be pointed out that they are exceedingly rare when one considers the extensive use of chick-embryo vaccines in the Army.

Because of the possible danger, however, it is important to determine whether an individual has a past history of allergy or is sensitive to egg or chicken. In this event, appropriate skin-tests should be performed before the administration of vaccine.

In allergic or egg-sensitive individuals the administration of a concentrated washed suspension of typhus rickettsiae might be used as vaccine since Coulson and Stevens⁶ have shown that these suspensions are relatively free of egg-antigens and Stull⁷ has shown that these suspensions did not induce skin-reactions in sites passively sensitized with sera from egg-sensitive patients.

³ These two cases were reported to the Division of Preventive Medicine, SGO.

⁴ Reported to the Division of Virus & Rickettsial Diseases, AMS.

⁵ Report to the Surgeon General, 19 January 1944.

⁶ See section II of these reports.

⁷ See section III of these reports.

EXPERIMENTAL

Skin-sensitivity following the subcutaneous inoculation of typhus-vaccine

Skin-tests were performed on 180 normal adults as follows: before inoculation with typhus-vaccine, one week after the second subcutaneous dose, and again two and four weeks following the third dose. All individuals who showed skin-sensitivity were again skin tested six, eight, and twelve weeks following the three doses of vaccine (1.0 ml subcutaneously on three successive weeks.)

Skin-tests were performed with the following antigens. Normal egg-yolk and egg-white were diluted in sterile salt solution to make a concentration of 0.01 mg N per ml. Each of the typhus-vaccines tested was likewise diluted in sterile saline to give a concentration of 0.01 mg N per ml. Sterile saline was employed as a control with each skin-test.

TABLE 1

GROUP (30 INDIVIDUALS IN EACH GROUP)	VACCINE	NO. OF SUBJECTS DEVELOPING SKIN SENSITIVITY TO:			
		Vaccine	Egg yolk & vac.	Egg yolk & egg white	Egg yolk & white & vac.
1	A Commercial†	0	0	0	0
2	B Commercial	3	1	0	0
3	C Commercial	0	2	0	1
4	D-A.M.S.†	1	1	1	0
5	No vaccine (control)	0	0	0	0
6	E-A.M.S.†	0	0	0	1
Total of all groups.....		4	4	1	2

* The author wishes to thank Dr. L. Julianelle, Dr. M. Siegel and Capt. S. Bukantz for having performed these tests.

† Typhus vaccine prepared at the Army Medical School.

‡ The three commercial typhus vaccines employed were prepared by different concerns.

An endermal injection of 0.1 ml of each of the above antigens (egg-yolk, egg-white, typhus-vaccine, and saline) was made at intervals of 5 cm on the flexor surface of the forearm of each subject. Reactions were read 15 minutes following injection as well as on the following two days. Positive reactions, when present, were always observed at the 15-minute reading, and had usually disappeared by the next day.⁸

Only one of 180 subjects tested before the administration of typhus-vaccine gave positive reactions to all of the skin test-antigens employed. The reactions in this subject were of moderate degree (3 x 3 cm erythema and 1 x 1 cm induration) occurring fifteen minutes following the endermal injection of typhus vaccine, egg-white and egg-yolk, respectively. This subject subsequently received the three weekly inoculations of 1.0 ml each of typhus-vaccine given subcutaneously without any systemic reaction. The development of skin-sensitivity following the administration of typhus-vaccine is indicated in table I.

* The author wishes to thank Dr. L. Julianelle, Dr. M. Siegel, and Capt. S. Bukantz for having performed these tests.

None of the subjects in the control-group (skin-tested but not inoculated with typhus-vaccine) showed evidence of skin-sensitivity to vaccine, egg-yolk, or egg-white. Of the 30 individuals who had received commercial typhus-vaccine A, none developed skin-sensitivity to the three antigens. Of the 30 individuals who received commercial typhus-vaccine B, three developed skin-sensitivity to vaccine alone, and one to both egg-yolk and vaccine. The remaining individuals of this group developed no skin-sensitivity to the three antigens. Of the 30 individuals who received commercial typhus-vaccine C, two developed skin-sensitivity to both egg-yolk and vaccine and one to egg-yolk, egg-white, and vaccine. The 27 remaining individuals of this group developed no skin-sensitivity. Of 30 individuals who received Army Medical School typhus vaccine D, one developed skin-sensitivity to vaccine alone, one to both egg-yolk and vaccine and one to egg-yolk and egg-white. The remaining 27 individuals of this group developed no skin-sensitivity to the three antigens used. Of 30 individuals receiving the Army Medical School vaccine E, only one developed skin-sensitivity to the three antigens used.

Of the 150 vaccinated subjects 1 or 0.65 per cent developed skin-sensitivity to the egg-antigens alone, 10 subjects or 6.7 per cent developed skin-sensitivity to vaccine; four of these or 2.7 per cent of the total being skin-sensitive to vaccine alone, while the remaining six (4 per cent of the total) were skin-sensitive to vaccine and the egg-antigens.

There is a difference in the number of subjects developing skin-sensitivity following the subcutaneous inoculation of typhus-vaccines originating from different sources. This is probably due to a variation in the product depending upon different technics used in the manufacture of the vaccines.

In 50 per cent of the sensitized subjects, skin-sensitivity was noted as early as two weeks following the first subcutaneous dose, or 1 week after the second dose, and in all cases four weeks after the third dose. The skin-reactions had become negative in seven of the 11 skin-sensitized individuals by the 12th week after the third subcutaneous dose of vaccine and this sensitivity had subsided considerably in two of the remaining four individuals. The subjects whose reactions remained relatively unchanged 12 weeks after the third dose of vaccine were the two who had become skin-sensitive to all three antigens. Despite the development of these skin-manifestations of sensitivity, none of the subjects in this series developed any significant systemic reaction to the subsequent subcutaneous inoculation of the whole vaccine in the prescribed dose.

DISCUSSION

The result of this study indicates that of 180 normal adults selected at random and skin-tested with typhus-vaccine, egg-white and egg-yolk, only one showed a moderate degree of skin-sensitivity to the three antigens used. When this subject subsequently received typhus-vaccine, by subcutaneous inoculation, no systemic reactions were observed. Even though 11 individuals did develop skin-sensitivity to either typhus-vaccine, egg-yolk or egg-white following the subcutaneous administration of typhus-vaccine, none developed a severe general

reaction when inoculated with typhus-vaccine at a later time. On the other hand, Major Arthur Stull⁹ did observe one instance in an individual with an allergic history where sensitivity was probably induced by the inoculation of an equine encephalomyelitic vaccine.

It should be pointed out that this study was performed on adults, in which group egg-sensitive individuals are relatively infrequent. The Army, too, represents a selected adult population. While the reactions observed in this group were rare, some severe reactions have been reported following the subcutaneous administration of typhus-, Rocky Mountain spotted-fever, yellow-fever or influenzal vaccines in individuals with an allergic history. The possible risk involved may be greater in the use of these vaccines in an unselected population, particularly in children, in which group a greater number of egg-sensitive individuals may be encountered.

SUMMARY

1. Only one of 180 normal adults skin-tested with typhus-vaccines, egg-white or egg-yolk showed evidence of skin-sensitivity to the three antigens. This individual when subsequently inoculated subcutaneously with typhus-vaccine developed no systemic reaction.

2. Of 150 adults receiving three subcutaneous doses of typhus-vaccine, four individuals developed skin-sensitivity to the whole typhus-vaccine alone, four to both egg-yolk and typhus-vaccine, one to both egg-yolk and egg-white and one to egg-yolk, egg-white and typhus-vaccine. None of these subjects developed a general reaction when subsequently inoculated with typhus-vaccine.

3. In spite of the fact that many millions of soldiers have received egg-embryo vaccines, the number of severe reactions known to have occurred following their use has been minimal. Some severe reactions have occurred however when vaccines were administered to egg-sensitive individuals. The risk is probably greater in children, in which group more egg-sensitive individuals may be encountered. It is considered advisable therefore to be cautious in the administration of egg-vaccines to allergic or egg-sensitive individuals. The use of concentrated washed rickettsial suspensions which are relatively free of egg-antigens could be used as vaccine in these cases.

The references cited in this section will be found at the end of section III of these reports.

⁹ See Section III of these reports.