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Reactions to tetanus toxoid*

By W. G. WHITE, G. M. BARNES and E. BARKER
British Leyland (Austin–Morris) Ltd., Cowley, Oxford
D. GALL, P. KNIGHT and A. H. GRIFFITH
Wellcome Research Laboratories, Beckenham, Kent
and R. M. MORRIS-OWEN and J. W. G. SMITH†
Radcliffe Infirmary, Oxford

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SUMMARY

In a factory population the occurrence of reactions to tetanus toxoid was recorded after 6740 injections. The incidence of general reactions was 0·3 % and of local reactions 2·6 %. The local reaction rate to the first injection of the basic immunization course was 0·9 %, to the second injection 2·7 %, and to the third injection 7·4 %. To booster injections the rate was 1·6 %. The local reaction rate was appreciably higher in women than in men – 14·4 % and 5·7 % respectively in the case of the third injection – and the incidence among women increased with age.

Tetanus vaccine containing 10 Lf of toxoid caused fewer reactions than one containing 20 Lf, but a reduction in the content of aluminium adjuvant did not affect the reaction rate.

Almost all reactors were found to have a satisfactory serum antitoxin concentration at the time of the reaction or developed a satisfactory immunity within 1–6 months.

Skin tests were made in 32 hypersensitive patients. Neither the diluent, thiomersal preservative, nor the culture medium appeared to be responsible for hypersensitivity. The degree of hypersensitivity elicited by a special highly purified toxoid was only very slightly less than that elicited by the commercially pure toxoid. It is suggested that reactions are largely due to the toxoid antigen itself rather than to impurities or other components of the vaccine.

INTRODUCTION

Although tetanus toxoid is a safe vaccine it has become evident in recent years that its injection is sometimes followed by an adverse reaction (Whittingham, 1940; White & Ungar, 1967; Edsall *et al.* 1967; Fardon, 1967). Whilst severe reactions are rare the development of a painful, swollen area after immunization

* Requests for reprints to Dr J. W. G. Smith.
† Present address: Epidemiological Research Laboratory, Central Public Health Laboratory, Colindale Avenue, London, NW9 5HT.

is quite common and does deter people from accepting the vaccine, particularly in a factory or similar environment, where a vaccination procedure can quickly acquire a bad reputation (Griffith, 1967; Yeager, 1967). For this reason we have studied the occurrence of reactions to tetanus toxoid and have attempted to evaluate the role of some of the factors responsible for their development.

MATERIALS AND METHODS

Vaccines and immunization procedures

The tetanus vaccines were aluminium hydroxide-adsorbed preparations (Tet/Vac/PTAH. B.P.) made by the Wellcome Research Laboratories. The three vaccines used contained in each 0·5 ml. dose (1) 0·65 mg. of aluminium ion and 20 Lf of toxoid, (2) 0·65 mg. of aluminium ion and 10 Lf of toxoid, (3) 0·3 mg. of aluminium ion and 10 Lf of toxoid. The different vaccines were given in monthly rotation, each new individual presenting within a given month being started on the same vaccine. Each subject received the same vaccine throughout his course of immunization. An adsorbed toxoid was also prepared containing a specially reduced amount of antigen – 2 Lf toxoid and 0·59 mg. aluminium ion per dose – for use in completion of the course of immunization in reactors.

The subjects, whose ages ranged from 15 to 65 years, all worked at the British Leyland (Austin–Morris) Ltd. factories in Oxford and Abingdon. A history of previous immunization is recorded routinely for all employees, together with details of service in the Armed Forces. It was assumed that such service had led to immunization against tetanus except in those who had served in the British Army between 1945 and 1949 and in the Royal Navy between 1945 and 1958, during which periods tetanus immunization was not officially practised (Ministry of Defence, personal communication). It was also established that since 1960 the injection given at the local hospital at the time of injury has been tetanus toxoid (J. C. Scott, personal communication).

The basic immunization course consisted of three intra-muscular doses of vaccine, spaced with an interval of 6 weeks between the first and second doses and 6 months between the second and third. Booster injections include (*a*) those given at the time of injury to previously immunized patients who had not received a toxoid injection within the previous 12 months, and (*b*) injections given to reinforce immunity in persons who had had the basic course of injections of plain toxoid more than 3 years earlier (White *et al.* 1969). All injections were given by the sisters and nursing staff. A full basic course of immunization was offered to unimmunized employees and also to those immunized more than 20 years previously, those with a vague history of immunization and those with an incomplete history of immunization more than 3 years previously. It should be pointed out that during the period of this study the duration of immunity against tetanus became more clearly defined, and nowadays many workers would agree that those immunized even more than 20 years previously need only have one injection of toxoid in order to boost their waning immunity, and that booster injections at the time of injury are probably unnecessary for perhaps some years after a previous

booster or full course of immunization (Rubbo, 1966; Scheibel, Bentzon, Christensen & Biering, 1966; Adams, Laurence & Smith, 1969; Peebles, Levine, Eldred & Edsall, 1969).

Reactions

The employees were asked to note and report whether any untoward effect occurred after immunization with tetanus toxoid. They were also asked to return to the medical centre 48 hr. after immunization, whether they had a reaction or not, when they were questioned regarding adverse reactions, and the site of injection was examined. We believe that very few patients with reactions were not seen after immunization. Local reactions were examined and the diameters of the areas of induration and of erythema measured using a transparent rule. Reactors were kept under observation until they were free from symptoms, all visible signs had disappeared and no local tenderness was present.

Local reactions were classified in the following way:

(*a*) 'Severe' – when an area of redness and/or oedema greater than 12 cm. in diameter was present at the injection site.

(*b*) 'Moderate' – when an area of redness and/or oedema of between 2 and 12 cm. in diameter was present.

(*c*) 'Negligible' – when an area of less than 2 cm. in diameter was involved. 'Negligible' reactions occurred very rarely; patients either developed a reaction greater in diameter than 2 cm. or developed no visible reaction at all. This category has been ignored in reactions rates quoted in this study.

General reactions were recorded when any untoward symptom was reported, other than those referable to the injection site.

Blood samples

Blood samples were taken for tetanus antitoxin titration:

(*a*) During the basic immunization course from about 1 in 20 of the subjects who were selected randomly. Samples were collected from each of these subjects (1) one week after the first injection, (2) immediately before the second injection, (3) immediately before the third injection and (4) one month later.

(*b*) In patients who had an adverse reaction (1) at the time of the injection or up to 1 week later, (2) one month after the injection or up to 6 months later.

The serum antitoxin concentrations were measured by the method of Glenny & Stevens (1938). In calculating the geometric mean serum antitoxin concentration, less than 0·01 unit/ml. was taken to be 0·007 unit/ml.

Skin tests

Skin tests were made by intradermal injection of approximately 0·01 ml. of the test material – a volume sufficient to give a small clearly visible bleb. Each subject was tested with four injections given at the corners of an imaginary square about $2\frac{1}{2}$ in. wide on the flexor surface of one forearm. The four skin test materials were prepared by the Wellcome Research Laboratories and consisted of:

(1) Vaccine diluent. Sodium borate–succinic acid buffer at ph 6·8, containing thiomersal 1/10,000 as a preservative.

(2) 'Commercial' toxoid. This material is tetanus vaccine in simple solution, B.P. (Wellcome, PX 191C), and is prepared by toxoiding a culture filtrate of *Clostridium tetani*. The toxoid is purified and concentrated and then diluted to 45 Lf/ml. with vaccine diluent. The preparation contained 58 μg. total nitrogen and 33 μg. macromolecular nitrogen per ml.

(3) 'Medium.' Sterile, uninoculated Mueller medium (PX 191B) (Fisek, Mueller & Miller, 1954), processed in a manner identical to the culture filtrate above. It contained 47 μg. total nitrogen and 33 μg. macromolecular nitrogen per ml.

(4) 'Purified' toxoid (PX 191D). This material was prepared by purifying and concentrating the toxin from a *Cl. tetani* culture lysate. The purified toxin was then toxoided and contained 30 μg. total nitrogen and 22 μg. macromolecular nitrogen per ml. when diluted to contain 45 Lf of toxoid per ml.

The skin test sites were observed and the diameters of any resulting areas of induration and of erythema measured with a transparent plastic rule at 30 min. and at 6, 24 and 48 hr. after injection. Skin reactions of less than 3 mm. in diameter were recorded as 0 mm.

RESULTS

General reactions

Only 22 out of 6740 injections (0·3%) were followed by general symptoms. In each case the symptoms developed within 6 hr. of injection and were influenza-like, with headache, lethargy and aching limbs. No general reactions were seen later than 6 hr. after injection and no delayed illness such as serum sickness. No reactions resembling anaphylaxis were seen. In not one instance were we able to decide with certainty that the general reaction genuinely represented hypersensitivity to the toxoid, but they did occur within 6 hr. of the injection, and 10 of the 22 patients also had a local reaction, so that the influenza-like symptoms may well have represented a form of generalized hypersensitivity. One patient had an exacerbation of his asthma within a few hours of a booster injection. One other had a local reaction over the site of his first injection, 6 hr. after his second injection was given into the opposite arm.

Local reactions

Of 6740 injections, 172 (2·6%) were followed by a local reaction greater than 2 cm. in diameter. Of the reactions, 139 were 'moderate', with an area of redness and/or swelling 2–12 cm. in diameter, causing only mild discomfort in the injected arm. Thirty-three patients (0·5%) had 'severe' reactions that measured between 12 and 30 cm. in diameter. The 'severe' reactions were painful and two of the patients had to be put off work for 48 hr. before the swelling and erythema settled under treatment with antihistamine and analgesic. Eight female patients developed a hard, tender swelling at the injection site during the week after immunization – four of these patients were treated with cloxacillin and, whether due to the treatment or not, the swelling subsided in about 7 days.

Table 1. *Incidence of local reactions to adsorbed tetanus toxoid*

	Injections in basic immunization course												Booster injections			
	1st				2nd				3rd							
	No. of injections	No. of reactions	%	S.E.* (%)	No. of injections	No. of reactions	%	S.E. (%)	No. of injections	No. of reactions	%	S.E. (%)	No. of injections	No. of reactions	%	S.E. (%)
Male	1493	6	0·4	0·2	1345	27	2·0	0·4	826	47	5·7	0·8	2025	30	1·5	0·3
Female	379	10	2·6	0·8	343	19	5·5	1·2	195	28	14·4	2·5	134	5	3·7	1·6
Total	1872	16	0·9	0·2	1688	46	2·7	0·4	1021	75	7·4	0·8	2159	35	1·6	0·3

Table 2. *Incidence of local reactions to adsorbed tetanus toxoid by age and sex*

	Men				Women			
Age	No. of injections	No. of reactions	%	S.E.* (%)	No. of injections	No. of reactions	%	S.E. (%)
15–20	320	8	2·5	0·9	205	7	3·4	1·3
21–30	992	23	2·3	0·5	277	15	5·4	1·4
31–40	672	16	2·4	0·6	160	11	6·9	2·0
41–50	813	10	1·2	0·4	166	12	7·2	2·0
51–60	668	16	2·4	0·6	140	11	7·9	2·3
Over 60	331	7	2·1	0·8	6	0	—	—

* S.E. = standard error.

Most reactions developed within 48 hr. of immunization, usually between 12 and 24 hr. Only three reactions appeared between 48 hr. and 7 days of immunization. The reactions remained at the maximum size for about 12–24 hr. and then slowly subsided to disappear in 2 or 3 days. In 11 patients, however, the local reactions showed a progressive further enlargement and were maximal 7–14 days after immunization.

The incidence of local reactions to each of the doses of toxoid is given in Table 1. Only the first occurrence of a reaction is recorded and patients who had a reaction did not normally complete their courses, unless their serum antitoxin proved to be unduly low. The true incidence of reactions to second and third injections is therefore likely to be higher than recorded in Table 1. The incidence of reactions increased with each dose of the basic immunization course and was highest after the third dose (7·4 %), but fell to a lower level (1·6 %) with booster doses.

It may be seen that reactions sometimes occurred after the first injection of tetanus toxoid. Of 16 reactions recorded to the first injection, 6 were beyond reasonable doubt genuinely to the first dose of toxoid, the patients having had less than 0·01 unit of antitoxin/ml. of serum 8–12 days after the injection. Of these 6 reactions, 5 were late, being maximal at 7–14 days after the injection.

The reaction rate in females was found to be more than twice as high as in males. Of the 16 reactors to the first injection 10 were female, and of the 11 patients whose reactions were maximal 7–14 days after the injection, 8 were female.

In Table 1 no distinction is made between individuals who had an incomplete or vague history of previous immunization and those with no history of previous immunization. To discover whether these two categories of subjects had different rates, a random sample of 1000 injections was re-examined and corrected rates calculated for those with some previous immunization and for those with none. The reaction rate was slightly higher among those with no previous immunization histories, but the difference was not significant. Partial immunization some years previously was therefore not found to increase reaction rates in the present study.

Table 2 records the incidence of reactions to the toxoids by age and sex. In women the reaction rate increased steadily with age, whereas in men the rate remained unchanged.

Analysis of the incidence of reactions by season and sex is shown in Table 3. The incidence in females fluctuated much more widely than in males, the highest incidence being nearly 9 % in the April–June quarter, and the lowest being 2·4 % in the July–September quarter. In males the incidence showed no significant seasonal change, being 2·5 % in April–June and 1·4 % in July–September.

A comparison of the incidence of reactions to the three vaccines, containing different amounts of toxoid and adjuvant, is shown in Table 4. When the differences between the reaction rates recorded in Table 4 were tested for significance by the method of Cochran (1954) it was found that vaccine containing 10 Lf caused significantly fewer local reactions than vaccine containing 20 Lf per dose ($P < 0·05$). A reduced content of aluminium adjuvant caused no further significant improvement.

The antitoxin response to the three toxoids is recorded in Table 5. It may be

Table 3. *Incidence of reactions to adsorbed tetanus toxoid by season and by sex*

	Men				Women			
	No. of injections	No. of reactions	%	S.E.* (%)	No. of injections	No. of reactions	%	S.E. (%)
Jan.–Mar.	986	22	2·2	0·5	208	13	6·3	1·7
Apr.–June	1695	42	2·5	0·4	297	26	8·8	1·6
July–Sept.	1780	24	1·4	0·3	339	8	2·4	0·8
Oct.–Dec.	1418	22	1·6	0·3	237	16	6·8	1·6

* S.E. = standard error.

Table 4. *Incidence of local reactions to different toxoid preparations*

			Injections in basic immunization course									Booster injections			All injections		
			First			Second			Third								
Toxoid	Aluminium ion content (mg. in dose of 0·5 ml.)	Toxoid content (Lf in dose of 0·5 ml.)	No. of injections	No. of reactions	%	No. of injections	No. of reactions	%	No. of injections	No. of reactions	%	No. of injections	No. of reactions	%	No. of injections	No. of reactions	%
1	0·65	20	111	2	1·8	110	5	4·6	97	4	4·1	125	4	3·2	443	15	3·4
2	0·65	10	453	3	0·7	379	7	1·9	209	5	2·4	674	11	1·6	1715	26	1·5
3	0·3	10	387	4	1·0	310	6	1·9	198	4	2·0	576	11	1·9	1471	25	1·7

Table 5. *Serum antitoxin response to different toxoid preparations*

Toxoid	Aluminium ion content of 0·5 ml. dose (mg.)	Toxoid content of 0·5 ml. dose (Lf)	Relation to basic immunization course: 6 weeks after 1st dose — No. of persons	6 weeks after 1st dose — G.M.T.*	6 months after 2nd dose — No. of persons	6 months after 2nd dose — G.M.T.*	1 month after 3rd dose — No. of persons	1 month after 3rd dose — G.M.T.*
1	0·65	20	21	0.06	17	0.33	20	10.8
2	0·65	10	52	0.03	42	0.16	43	5.3
3	0·3	10	70	0.02	64	0.14	59	4.8

* G.M.T. = geometric mean antitoxin concentration.

Table 6. *Distribution of serum tetanus antitoxin concentration in reactors and matched non-reactors*

Time of antitoxin titration	Subjects	No. of subjects	% with a serum antitoxin concentration (unit/ml.) of: <0·01	0·01–	0·1–	1·0–	10–100	Geom. mean serum antitoxin (unit/ml.)
(A) At or up to 1 week after injection	Male reactors	81	7	11	37	34	11	0·66
	Female reactors	33	30	18	34	15	3	0·10
	Total reactors	114	14	13	36	28	9	0·38
(B) At time of reaction or up to 1 week later	Reactors	68	16	15	35	28	6	0·31
	Matched non-reactors	68	25	22	40	12	1	0·09
(C) At 1 month after reaction or up to 6 months later	Reactors	62	0	5	13	48	34	3·6
	Matched non-reactors	62	2	6	26	39	27	2·2

seen that reduction in the Lf content of the vaccine was accompanied by some diminution in the response to each dose of the basic immunization course. The diminution is significant by the t test at the 2% level in the case of the response to the first dose, and at the 5% level in the responses to the second and third doses. A reduction in the content of aluminium adjuvant caused no further significant change in the antitoxin response.

Immune status of reactors

Most of the individuals who had a local reaction to tetanus toxoid were found to have a high serum antitoxin at the time of reaction, but this was not always the case. Table 6A shows that although 73% of reactors had 0·1 unit of antitoxin/ml. of serum or more, 14% had less than 0·01 unit/ml. When reactors were compared with non-reactor controls, carefully matched for age, sex, stage of immunization, vaccine and month in which the vaccine was given (of the 114 reactors whose antitoxin at the time of reaction were known, 68 could be matched), the mean serum antitoxin of reactors was more than three times higher than that of controls (Table 6B).

The possibility was considered that the 14% of reactors who had less than 0·01 unit of antitoxin/ml. of serum might have been in the process of developing a satisfactory antitoxin response. It can be seen in Table 6C that all of 62 matched reactors had more than 0·01 unit/ml. of antitoxin 1–6 months after the injection which had caused a reaction. Antitoxin titrations were also made in another 46 reactors who were not matched, and all but one had over 0·01 unit/ml. of serum 1–6 months after the toxoid injection. The one patient who produced no antitoxin was a female, whose reaction to her first dose of toxoid reached its maximum size ($5 \times 2{\cdot}3$ cm. erythema and 2×1 cm. induration) 13 days after the injection. Four weeks later her serum antitoxin was still less than 0·01 unit/ml.

Some evidence was obtained that the serum antitoxin concentration may rise more rapidly in persons who react to toxoid than in those who do not. When tested 6 weeks after the first injection of toxoid 11 out of 15 reactors (73%) showed a serum antitoxin rise from less than 0·01 unit/ml. to 0·1 unit/ml. or more, whereas only 20 of 104 non-reactors (19%) showed a similar rise. The difference is highly significant ($P = 0{\cdot}00005$). Two reactors showed a rise in their serum antitoxin concentration from 0·01 and 0·02 unit/ml. respectively to 50 units/ml. within a month after injection.

Although the incidence of reactions differed in men and women, and in women of different ages, no similar variation in the antitoxin responses could be detected.

Low dose toxoid

The reduced dose of adsorbed toxoid (2 Lf per dose) has so far been used to complete the course of immunization in 25 reactors. Only 2 of the 25 experienced an adverse response; they were females who had had both a moderate local reaction and generalized symptoms following full-dose toxoid. In these two

patients the low dose preparation caused local reactions with erythema of 7·5 cm. and 2·5 cm. diameter respectively and no generalized symptoms. The serum antitoxin concentrations in the 25 subjects 1 month after the reduced dose were highly satisfactory, having risen from a mean of 0·23 unit/ml. to 5·0 units/ml. with a range of from 1 to 20 units/ml.

Skin tests

Skin tests were made in 32 patients who had developed local reactions of varying severity to an immunizing injection of tetanus toxoid between 3 months and 8 years previously. The two skin-test toxoids were injected in a dilution of 1/20, 1/50, 1/200 or 1/500 according to the severity of the reaction the patient had experienced. One patient, who had had a very small reaction, was tested with undiluted skin-test material, 20 patients with 1/20, 4 with 1/50, 5 with 1/200 and 2 patients, who had had severe reactions to immunization, with 1/500 dilutions.

Two patterns of response to skin-testing were observed:

(*a*) A wheal and flare response which reached a peak at 20–30 min. and then faded slowly and completely – in no patient was any reaction visible at 6 hr.

(*b*) A delayed response consisting of erythema with induration, reaching a peak at about 24 hr.

It is probable that the 30 min. response represents reagin-mediated hypersensitivity, and the 24 hr. response delayed-type hypersensitivity.

In Tables 7 and 8 the results are given in terms of the diameters of the area of erythema at 30 min., and of induration at 24 hr. after injection of the test material; the mean diameters given are calculated from the tests at all dilutions, because there was no significant difference between the means among patients tested with the different strengths of skin-test toxoids.

Skin tests with the thiomersal-containing vaccine diluent and with the 'medium' caused negligible responses in the 32 patients who had previously reacted to an immunizing dose of toxoid. Only two patients responded to the diluent and four to the broth and in each case the responses were small and consisted of a wheal and flare with no delayed component.

All except one of the patients showed a positive response to skin testing with both toxoid preparations. Most of the subjects developed both an immediate and a delayed response, but seven had only an immediate response and four patients only a delayed response. The reactions to the 'purified' toxoid were, in general, slightly smaller than those obtained with the 'commercial' toxoid, and in two patients a small delayed response occurred to the 'commercial' toxoid only.

Skin tests were also made in nine subjects who had been immunized with toxoid but had shown no reaction, and in five unimmunized persons. In these control subjects the skin-test toxoids were injected undiluted (Table 8). Immediate hypersensitivity to the diluent was apparent in one of the non-reactor controls and one of the unimmunized control subjects, but no delayed hypersensitivity was detected. A response to the 'medium' occurred in 6 of the 9 non-reactors and 2 of the 5 previously non-immunized subjects; this reactivity also was only of the immediate type. Delayed hypersensitivity to the toxoid was present in 4 of the 9

Table 7. *Local reactions to skin testing in 32 hypersensitive patients*

Skin-test material	Erythema at 30 min.				Induration at 24 hr.			
	Diluent	'Medium'	'Purified' toxoid*	'Commercial' toxoid*	Diluent	'Medium'	'Purified' toxoid*	'Commercial' toxoid*
No. of patients with a reaction to the test material	2	4	26	27	0	0	22	24
Mean diameter of reaction (mm.)	4	4	18	20	0	0	9	11

* The skin test toxoids injected in dilutions of 1/20 (20 patients), 1/50 (4 patients), 1/200 (5 patients) or 1/500 (2 patients), and undiluted in 1 patient, according to the degree of hypersensitivity present in each individual patient.

Table 8. *Local reactions to skin testing in controls: nine persons who had not reacted to toxoid and five previously non-immunized persons*

Skin-test material		Erythema at 30 min.				Induration at 24 hr.			
		Diluent	'Medium'	'Purified' toxoid*	'Commercial' toxoid*	Diluent	'Medium'	'Purified' toxoid*	'Commercial' toxoid*
Nine persons who had not reacted to toxoid	No. of persons with a reaction to the test material	1	6	4	5	0	0	3	4
	Mean diameter of reaction (mm.)	9	9	18	17	0	0	13	10
Five non-immunized persons	No. of persons with a reaction to the test material	1	2	2	2	0	0	0	0
	Mean diameter of reaction (mm.)	9	10	13	16	0	0	0	0

* The skin test toxoids were injected undiluted in all subjects.

immunized persons who had not previously reacted to toxoid injection, but in none of the non-immunized subjects.

DISCUSSION

The reactions encountered in this investigation were those arising during the course of immunizing and maintaining the immunity of a normal factory population. The incidence of reactions was appreciable, and occasional severe reactions, involving the whole upper arm or even the whole arm, prejudiced the success of the campaign.

We still do not know why certain individuals suffer these local reactions or what distinguishes them from non-reactors. There is an increasing predisposition to reactions with increasing immunization, though reactions sometimes occurred to the first injection of toxoid. The reaction rate to boosters was, however, lower than the general reaction rate, which suggests that the state of hypersensitivity revealed when toxoid is given in fairly closely spaced intervals wanes with the passage of time. In our series, known reactors were not given further full doses of toxoid so we have no cases where a reaction to an earlier dose was followed by no reaction to a later full dose. Dr R. G. Orr (personal communication), however, has several such well-documented cases and it is possible that hypersensitivity is sometimes quite short-lived. The high incidence of reactions to the third dose of the basic immunization course might therefore be reduced by adopting a 12-month interval between the second and third doses, rather than a 6-month interval, and we are examining this possibility.

Local reactions to adjuvant vaccines occur less frequently when injections are given intramuscularly rather than subcutaneously (Relihan, 1969; Snell & Burland, 1970), but none of the injections reported here were intentionally given subcutaneously. In this connexion, the greater incidence of reactions among females, and particularly older females, may partly be accounted for by the difficulty of giving them a true intramuscular injection owing to the presence of a deeper layer of subcutaneous fat and smaller muscle mass, although no correlation between depth of fat or muscle mass and reactions was sought in the study reported here. The lower incidence of reactions observed in the summer is unexplained – no other factor could be found to differ in the summer months, such as nursing staff, type of vaccine or effectiveness of follow-up.

The findings presented in Table 4 suggest that the amount of toxoid in tetanus vaccine is an important factor influencing the incidence of local reactions whereas the amount of aluminium adjuvant, within the range examined, was not important. Reduction in the content of toxoid in tetanus vaccine may therefore be a practical way of reducing the reaction rate, although this may be accompanied by some reduction in the antitoxin response (Table 5). Nevertheless, the response induced by the adsorbed vaccine containing 10 Lf of toxoid remained very satisfactory, and such a preparation might therefore be preferred to one containing 20 Lf for routine use.

Patients who react to an injection of toxoid present a problem regarding the

completion of their course of immunization. The examination of the immune status of reactors showed that whilst most had a high serum antitoxin at the time of their reaction, 14% could be regarded as non-immune. Furthermore, whilst the reactors may have a more rapid antitoxin response than non-reactors, the development of circulating antitoxin cannot be regarded as certain, since one of 108 reactors was still unprotected 4 weeks later, although the patient was one of the few who had reacted to the first dose of toxoid. The use of a rapid, easily performed *in vitro* method of antitoxin estimation would be of great value to identify such patients. In the absence of such a technique our findings confirm those of McComb & Levine (1961) and Trinca (1963), that it is possible to avoid further significant reactions and confidently expect the development of a satisfactory antitoxin response in hypersensitive patients by using a small dose of toxoid – for example, 2 Lf. A somewhat different approach has been recommended by Gross, Bartels, Körner & Kindt (1970), who found that the use of plain (non-adsorbed) toxoid for third and booster injections was attended by reduced reaction rates.

A high proportion of those who had had a local reaction to immunization with tetanus toxoid responded to skin testing with toxoid, developing both a wheal-and-flare and a delayed response. A small proportion developed only an immediate reaction or only a delayed reaction to the skin testing, and only 1 of 32 patients had no response. However, a response was not confined to those who had reacted adversely to immunization, because about half the non-reactors tested also responded to the skin tests. It is unlikely therefore that a response to skin testing could be used to forecast which patients might react adversely to vaccination with tetanus toxoid.

The skin-test reaction to the highly purified toxoid was slightly less than that to the commercially purified toxoid, but the difference was small and it seems unlikely that a significant reduction in the reaction rate, or in the severity of local reactions, would follow further purification of tetanus toxoid. A response to skin testing with the thiomersal-containing diluent and to the processed culture medium was uncommon among the reactors and, when it was observed, the response obtained was small and had no delayed component, suggesting that neither is a significant factor in causing reactions to toxoid vaccine. Reactions to thiomersal in skin-test materials are known to occur (Reisman, 1969; Hansson & Möller, 1971*a*), but are not believed to be of importance in determining the development of a reaction to toxoid (Hansson & Möller, 1971*b*). The skin test findings suggest that reactions may largely be caused by the toxoid antigen itself rather than by impurities in the vaccine.

An unexpected observation was the relatively high proportion of the control subjects who showed a reaction to skin-testing with the 'medium'. This reactivity had no delayed component, but it is difficult to explain why a similar response was not seen more frequently in the hypersensitive subjects. It is possible that the reactivity to the toxoids injected about 2½ in. away in the forearm might have impaired a response to the adjacent 'medium'.

In the light of the findings we have discussed, the measures useful in reducing reactions may be summarized as follows:

(1) Accurate recording of immunization histories so that unnecessary courses of immunization and unnecessary booster doses may be avoided.

(2) The use of tetanus vaccine containing 10 Lf of toxoid rather than 20 Lf.

(3) The use of the intramuscular route of injection.

(4) The use of reduced doses of toxoid, e.g. 2 Lf, for those who have previously reacted adversely.

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