RESPONSE TO TWO SMALL DOSES OF TETANUS TOXOID SINGLY OR COMBINED AS DT OR DTP

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DURING the past 20 years we have studied the response to single and multiple antigen preparations in both institutionalized and noninstitutionalized subjects (*1–4*). In 1943–44, individuals in several of the study institutions were inoculated with different antigens: diphtheria and tetanus toxoids, typhoid and pertussis vaccines, and scarlet fever toxin, singly or in various combinations. Many of the subjects were still available in 1958 for a followup study to determine their response to a booster injection of some of the antigens.

Among the individuals were 19 from an institution for the mentally retarded with a record of no previous injections of tetanus toxoid. These were studied for their response to small doses of tetanus toxoid or an antigen containing tetanus toxoid. They were given two 0.2-ml. intramuscular injections of adsorbed tetanus toxoid, either singly or combined with another antigen, 2 years apart. In 17 of the 19 subjects, the injections were followed by high serum antitoxin titers. Because the results were so favorable, they were made the subject of this report.

The material injected and the test methods used were described in an earlier report (*5*), and pertinent information is given in table 1. The subjects, of both sexes, were residents of the same institution; their ages ranged between 21 and 27 years.

The first injection in 7 of the 19 subjects was diphtheria and tetanus toxoids and pertussis vaccine combined (DTP), aluminum phosphate adsorbed; in 7 it was diphtheria and tetanus toxoids (DT), aluminum phosphate adsorbed, and in 5 it was tetanus toxoid, aluminum phosphate adsorbed. In all 19 the second injection, 2 years later, was DT (table 2).

The serum antitoxin titers before and after administration of the two doses are also shown in table 2, with material injected, sex of the subjects, and age at time of first injection.

After the first injection three of the seven subjects who received DTP had tetanus anti-

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Table 1. Antigens used for immunization: Lf, purity, aluminum phosphate content, and antigenicity in guinea pigs

Antigen	Tetanus component			
	Lf in 0.2 ml.	Purity (Lf per mg. protein nitrogen)	Aluminum phosphate (mg. aluminum in 0.2 ml.)	Units of antitoxin by guinea pig test [1]
DTP	2	1,508	0.11	5
DT	2	1,603	.23	4
T	1.4	1,683	.25	6

[1] 0.5 ml. injected in the guinea pig antigenicity test.

Table 2. Tetanus antitoxin titers and sex, age, and previous inoculation history in subjects given two intramuscular 0.2-ml. doses of DTP, DT, or tetanus toxoid only

Subject No.	Sex, age	Serum titer before first dose	Antigen injected (first dose) 0.2 ml.	Tetanus antitoxin titers after first dose					Antigen injected (second dose) 0.2 ml.	Tetanus antitoxin titers after second dose	
				1 week	2 weeks	8 weeks	1 year	2 years		2 weeks	8 weeks
6	F, 27	<0.001	DTP	<0.001	<0.001	<0.001	<0.001	<0.001	DT	3	0.6
2640	M, 24	<.001	DTP	<.001	<.001	<.001	<.001	<.001	DT	3	.6
2656	M, 24	<.001	DTP	<.001	<.001	<.001	<.001	<.001	DT	3	.6
2657	M, 22	<.001	DTP	<.001	<.001	<.001	.003	.003	DT	3	3
2660	M, 21	<.001	DTP	<.001	<.001	.03	.03	.03	DT	30	7.5
2666	M, 26	<.001	DTP	<.001	<.001	.003	.03	.01	DT	3	3
2671	M, 22	<.001	DTP	<.001	<.001	<.001	<.001	<.001	DT	3	3
2669	M, 25	<.001	DT	<.001	<.001	<.001	<.001	<.001	DT	7.5	3
2672	M, 22	<.001	DT	<.001	<.001	<.001	<.001	<.001	DT	3	3
2673	M, 25	<.001	DT	<.001	<.001	<.001	<.001	<.001	DT	3	3
2653	M, 23	<.001	DT	<.001	<.001	<.001	<.001	<.001	DT	3	3
2655	M, 23	<.001	DT	<.001	<.001	<.001	<.001	<.001	DT	3	3
9	F, 27	<.001	DT	<.001	<.001	<.001	<.001	<.001	DT	.2	.03
2664	M, 23	<.001	DT			<.001	<.001	<.001	DT	3	.06
1	F, 27	<.001	T	<.001	<.001	<.001	<.001	<.001	DT	.6	.06
3	F, 25	<.001	T	<.001	<.001	<.001	<.001	<.001	DT	3	
10	F, 27	<.001	T	<.001	<.001	<.001	<.001	<.001	DT	<.001	<.001
11	F, 26	<.001	T	<.001	<.001	<.001	<.001	<.001	DT	.6	.15
16	F, 25	<.001	T	<.001	<.001	<.001	<.001	<.001	DT	<.001	<.001

toxin titers of 0.003 to 0.03 units per milliliter of serum. None of those who received either DT or tetanus toxoid alone showed a measurable rise in tetanus antitoxin titer.

After the second injection, all the subjects whose first injection was either DTP or DT had tetanus antitoxin titers of 0.2 to 30 units per milliliter of serum, suggesting a secondary response even though only 2 Lf (Limes flocculation) units had been given. Of the five subjects who had received only tetanus toxoid as the first injection, three had 0.6 to 3 units of tetanus antitoxin, and two failed to respond.

Discussion

Although there were only a few subjects in this study, production of antibodies after the injection of two small doses of tetanus toxoid was striking. It would appear that the DTP, even though it contained a lower concentration of aluminum phosphate, less than half the quantity in DT and tetanus toxoid, produced the greatest antigenic response; three of the subjects responded with titers of 0.003 units or more of tetanus antitoxin after the first dose. Two years later, after the 0.2-ml. injection of DT, all seven of the individuals had titers of 3 units or more, and one responded with a titer of 30 units per milliliter. It is interesting that, after the initial dose, two subjects (2657 and 2666) appeared to reach peak response at 8 weeks to 1 year. The greater response in the subjects injected with DTP suggests an adjuvant effect of the pertussis component. Studies showing such an effect on the production of antitoxin in animals when pertussis antigen is mixed with diphtheria or tetanus toxoid have been reported. Levine and Stone (*6*) and Farthing (*7*) reviewed the literature on this subject.

Combining the diphtheria and tetanus toxoids appeared to produce a stronger antigen than the tetanus toxoids alone. Comparison is difficult because the two antigens varied in Lf units. The tetanus toxoid contained only 1.4 Lf units per dose, and the tetanus toxoid component in the DT contained 2 Lf units. Antigenicity tests in guinea pigs showed the two preparations to be of comparable potency (table 1). The only two subjects who failed to respond were in the group given tetanus toxoid alone as the first injection.

From the data presented, it should be pointed out that there were too few subjects to provide a basis for immunization schedules. As reported (*8*, *9*), there are a few persons who are

hyper-reactive to diphtheria or tetanus toxoid, and such persons can be boosted adequately with smaller doses (1 to 2 Lf units). Our data suggest that hyper-reactive persons may achieve primary immunization with smaller doses adequately spaced.

Other studies (*10–12*) indicate that wider spacing of doses results in a reinforced value of subsequent doses. This observation is of particular importance in immunization clinics. Frequently, elementary school students miss one or more regularly scheduled doses, and some physicians repeat the entire dosage schedule for them (*13–15*). Further, private physicians often extend dosage schedules for patients with acute respiratory infection or febrile illness. From the data presently available, it appears that the dosage schedule for primary immunization may be extended for at least 2 years without reducing the immunizing value of the standard immunizing dose. Further work needs to be done on the effect of extended dosage schedules when smaller amounts of antigen (1 to 2 Lf units) are given.

While the data suggest possible differences in response between males and females, the number studied was too small to warrant conclusions.

Summary

In a group of 19 young adults with no previous history of tetanus immunization, two small doses (total, 3.4 to 4 Lf units) of tetanus toxoid were given intramuscularly 2 years apart. The antigens were DTP, DT, or tetanus toxoid.

After the first injection of DTP, three of seven produced a detectable amount of tetanus antitoxin, but no response was elicited after the first injections of DT and tetanus toxoid. After the second injection of DT with the 2-year interval, all but 2 of the 19 showed titers in the range of 0.2 to 30 units of antitoxin—well above the accepted protective level of 0.01 to 0.05 units. The five subjects who received only the tetanus antigen as the first injection showed a lower response than those who received the tetanus toxoid as DT or DTP. Of the five, two had no measurable response.

These data suggest that further studies should be made to evaluate the use of smaller doses for primary immunization.

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