Antigenic Response to Booster Dose of Diphtheria and Tetanus Toxoids

Seven to thirteen years after primary inoculation of noninstitutionalized children

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FROM 1943 to 1950, in Saginaw County, Mich., 802 noninstitutionalized children 2–15 years of age were injected, in groups, with different combinations of diphtheria toxoid, tetanus toxoid, pertussis vaccine, typhoid vaccine, and scarlet fever toxin, according to defined dosage schedules. The children's reactions were studied and their specific immune response measured in terms of circulating antibody. The results formed the basis for a series of reports by Volk and associates (*1–4*).

From 7 to 13 years later blood specimens were taken from 174 of these subjects, now 13 to 20 years old, and each was then given an intramuscular "booster" injection of combined diphtheria and tetanus toxoids, aluminum phosphate adsorbed. Antibody titrations for diphtheria and tetanus antitoxin were made at six intervals following the booster injection, as described below.

The results of the antibody titrations before and after booster injection form the basis for this report. No known cases of diphtheria occurred in Saginaw County during the period covered by this study.

Methods

A registered nurse from the Saginaw County Health Department interviewed each subject and his parents for recollection or records of intervening booster injections and verified most reports from physician, clinic, or hospital records. The nurse also performed all of the inoculations and followups for reactions, drew

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Maud G. Gilbert, of the Saginaw County Health Department, and Frances Angela, of the Michigan Department of Health laboratories, gave technical assistance in the study.

This study was made in cooperation with the committee on multiple antigens, epidemiology section, American Public Health Association, and was supported in part by research grant E–1115 from the National Institute of Allergy and Infectious Diseases, Public Health Service.

all of the blood samples, and assisted in the tabulation of data.

The booster dose of antigen, a routine product of the division of laboratories, Michigan Department of Health, contained, in a dose of 0.2 ml., 2 Lf (Limes flocculation) units each of diphtheria and tetanus toxoids. The diphtheria toxoid had a purity of 1,648 Lf units per milligram of protein nitrogen. The tetanus toxoid had a purity of 1,603 Lf units per milligram of protein nitrogen. Each dose of 0.2 ml. also contained 0.23 mg. of aluminum in the form of aluminum phosphate. Antigenicity tests on the combined toxoids, performed according to the Minimum Requirements of the National Institutes of Health, produced in the guinea pig two to three units of diphtheria antitoxin per milliliter of serum and four to six units of tetanus antitoxin per milliliter of serum.

This booster dose of diphtheria and tetanus toxoids in 0.2 ml. amounts was chosen because preliminary exploration with a group of institutionalized adults indicated that this dosage gave prompt and vigorous response, free from any undesirable reactions. Pertussis antigen was not included in the booster dose because boosting immunity to pertussis was not considered to be important in teenagers and young adults.

The titration of each participant's serum was performed prior to the booster injection and at intervals after the injection of 1 and 2 weeks and 2, 6, 12, and 24 months. All serum titrations were performed in the Michigan Department of Health laboratories. The titrations for diphtheria antitoxin were made by the method of Fraser (*5*). Preliminary and final tests were made at the 0.01 unit level unless the preliminary tests showed that the value was below 0.01 unit. In such cases the serum was titrated at the 0.001 unit level. The reactions in rabbits which received the toxin and antitoxin mixtures were read after 72 hours. The amount of antitoxin in the serum was determined by that mixture which gave a reaction slightly less than the control mixture. If no such reaction was elicited, a value was derived from the mean of the dilution which gave no reaction and the next highest dilution which gave a reaction equal to or greater than the control.

Mice were used for the tetanus antitoxin titrations, one mouse for each dilution, and injections were made subcutaneously. Preliminary and final tests were made at the 0.01 unit level and if the values were less than 0.01 units the titration was carried out at the 0.001 unit level. The amount of antitoxin in the serum was calculated from the mixture which caused death in the test mice 1½ to 3 days later than in the control mice. If no deaths had occurred at this time, a mean titer was calculated as for the diphtheria antitoxin. This value was obtained from the mean dilution causing death 2½ days or more later than in the controls and the next highest dilution causing death at the same time as, or sooner than, in the controls.

Material from the same series of dilutions was used for both the diphtheria and tetanus antitoxin titrations. The preinoculation, 1-week, 2-week, and 2-month samples were run

Table 1. Diphtheria and tetanus antitoxin titers 7 to 13 years following primary inoculation series

Prebooster titers	Primary injection history								Total
	3 injections		2 injections		1 injection		Other (3 injections)		
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Diphtheria	109	100. 0	21	100	4	100	40	100. 0	174
<0.01	11	10. 0	5	24	1	25	9	22. 5	26
0.01–0.05	39	35. 8	7	33	1	25	5	12. 5	52
>0.05	59	54. 2	9	43	2	50	26	65. 0	96
Tetanus	100	100. 0	20	100	4	100	37	100. 0	161
<0.01	9	9. 0	7	35	2	50	10	27. 0	28
0.01–0.05	22	22. 0	4	20	0	0	5	13. 5	31
>0.05	69	69. 0	9	45	2	50	22	59. 5	102

simultaneously. The same reference standard lots of diphtheria and tetanus toxin respectively were used for all titrations.

Reactions

For 11 days following administration of the booster dose, 94 subjects were examined for evidence of local or general reactions. These examinations were performed by the same nurse who also had observed all of the reactions in the previous studies (*1*). Only mild and infrequent reactions were evoked by the 0.2-ml. dose. The 80 subjects who could not be observed were interviewed. Since these were teenagers and young adults, verbal information on the freedom from serious reaction was considered reliable. No "antigen cysts" (*4*) were observed in any of the persons receiving booster injections.

Results

As far as could be determined, none of the 174 persons available for study who had received primary inoculations between 1943 and 1950 had received an intervening diphtheria toxoid booster, but 13 had received a tetanus toxoid booster and were excluded from the tetanus evaluation. Uniformly the subjects were given a booster injection of 0.2 ml. of diphtheria and tetanus toxoids as described earlier. Four groupings (table 1) were made relative to the type of primary inoculation: 109 received three doses of DTP (diphtheria and tetanus toxoids and pertussis vaccine alum precipitated), appendix A; 21 received two doses of DTP, appendix B; 4 received one dose of DTP, appendix C; 40 received primary inoculations elsewhere by private physicians and a booster injection of DTP during 1949–50 (*3*), appendix D and the last group in table 1, identified

Table 2. Fold increase in diphtheria and tetanus antitoxin titers between the prebooster and highest observed titer following three primary injections of DTP, followed by DT boosters [1]

Prebooster range antitoxin units	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096	8,192	16,384	32,768	Total
0–<0.001:																	
Diphtheria													2				2
Tetanus											1						1
0.001–<0.01:																	
Diphtheria								1		2	2	4					9
Tetanus												3	2	2		1	8
0.01–<0.05:																	
Diphtheria						1		13	15	9	1						39
Tetanus								1	4	6	7	4					22
0.05–<0.2:																	
Diphtheria			1		4	3	10	7	5	2							32
Tetanus						1	3	3	14	12	2						35
0.2<1.0:																	
Diphtheria			2	2	8	3	2	1									18
Tetanus				1	2	1	8	5	3								20
1.0–<5.0:																	
Diphtheria	1	4	1	1	2												9
Tetanus	1	1	4	2	2	1											11
5.0–<10.0:																	
Diphtheria																	0
Tetanus		1															1
10–<20:																	
Diphtheria																	0
Tetanus		1															1
20–<40:																	
Diphtheria																	0
Tetanus																	0
40–<80:																	
Diphtheria																	0
Tetanus		1															1
Total:																	
Diphtheria	1	4	4	3	14	7	12	22	20	13	3	4	2				109
Tetanus	1	4	4	3	4	3	11	9	21	18	10	7	2	2		1	100

[1] DT, 0.2 ml. containing 2 Lf each of diphtheria and tetanus toxoids $AlPO_4$ adsorbed.

as "other." (See documentation note, page 194, for information on availability of appendix tables.)

Immunity Status

Table 1 presents a summary of the prebooster diphtheria and tetanus antitoxin titers for the four primary inoculation groups. The subjects are divided into three categories according to prebooster antitoxin titer: below 0.01 units, generally considered to be unprotected; 0.01 to 0.05 units, with probable protection; and greater than 0.05 units, generally accepted as protected.

The primary injection history refers to the number of injections during the previous study. The column head "Other (3 injections)" refers to subjects who received a three-dose primary inoculation series from private physicians but received a booster dose in 1949–50 (*3*) (appendixes A, B, C, and D).

Diphtheria titers. Of the 174 subjects studied for diphtheria antitoxin titers, 26 had titers below 0.01 units, 52, between 0.01 and 0.05 units; and 96, greater than 0.05 units.

Tetanus titers. Of 161 subjects studied for tetanus antitoxin titers, 28 had titers below 0.01 units; 31, between 0.01 and 0.05; and 102, greater than 0.05 units.

Antitoxin Response to Booster Dose

Table 2 presents the diphtheria and tetanus antitoxin response to a booster dose for the subjects who had received a primary course consisting of three injections of a multiple antigen containing diphtheria and tetanus toxoids (appendix A). The response is presented in terms of fold increase and represents the maximum multiple of the prebooster titer. This was usually observed at 2 weeks. When no 2-week sample was obtained, the 1-week or 2-month titer was used. Without exception, all subjects responded within 2 weeks and with antitoxin titers well above the generally accepted protective levels. In general, the lower the prebooster titer, the greater the fold increase in antitoxin titer. Subjects with a prebooster titer of 1.0 unit or more showed a lower fold increase.

Diphtheria titers. Of the 109 subjects

Table 3. Fold increase in diphtheria and tetanus antitoxin titers between the prebooster and highest observed titer following two primary injections of DTP, followed by DT booster [1]

Prebooster range antitoxin units	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096	8,192	16,384	32,768	Total
0–<0.001:																	
Diphtheria													1				1
Tetanus														1		1	2
0.001–<0.01:																	
Diphtheria										2		2					4
Tetanus										1	2	1	1				5
0.01<0.05:																	
Diphtheria							1	1	3	1		1					7
Tetanus								1	1	1	1						4
0.05–<0.2:																	
Diphtheria						1	3	1	1								6
Tetanus					1			2		1							4
0.2–<1.0:																	
Diphtheria			1			1											2
Tetanus								2									2
1.0–<5.0:																	
Diphtheria			1														1
Tetanus			1														1
5.0–<10:																	
Diphtheria																	0
Tetanus			1														1
10–<20:																	
Diphtheria																	0
Tetanus		1															1
Totals:																	
Diphtheria			2			2	4	2	4	3		3	1				21
Tetanus		1	2		1			5	1	3	3	1	1	1		1	20

[1] DT, 0.2 ml. containing 2 Lf each of diphtheria and tetanus toxoids $AlPO_4$ adsorbed.

studied, only 2 showed diphtheria antitoxin levels below 0.05 units at the end of 1 week and these had levels between 0.01 and 0.05 units. All others responded with titers above 0.05 units in 1 week. At 2 weeks all had titers of 0.6 units or higher.

Tetanus titers. Nine subjects (appendix A) were not included in the evaluation of tetanus response since they had received intervening boosters of tetanus toxoid. Of the remaining 100 subjects, 3 responded with tetanus antitoxin titers at the end of one week between 0.01 and 0.05 units. All others had 1-week titers above 0.05 units. At 2 weeks all had titers of 3.0 units or more (highest 140).

There were 18 subjects (appendix A) who showed a higher tetanus antitoxin titer at the time of booster injection than the last recorded titer following the primary series, in spite of the fact that as nearly as could be determined from the medical records, they had received no intervening booster doses. This can hardly be explained on the basis of natural tetanus boosting, hence it would appear that the seven subjects with tenfold or greater increases might have received a toxoid booster unknown to the investigators. For the subjects with less than tenfold rises in titer, a possible explanation is the fact that the titrations were performed by different personnel in different laboratories 7–13 years apart.

Table 3 presents the diphtheria and tetanus antitoxin response to a booster dose for the group which had received two doses of multiple antigen 7–12 years earlier (appendix B).

Diphtheria titers. Of the 21 subjects studied, all responded within 2 weeks with diphtheria titers well above protective levels. The response to booster injection was similar to that observed in subjects who had received a three-dose primary series.

Tetanus titers. Of 20 subjects studied, all responded within 2 weeks with tetanus antitoxin titers well above protective levels. The response to a booster injection of tetanus toxoid in this group was very similar to that observed

Table 4. Fold increase in diphtheria and tetanus antitoxin titers between the prebooster and highest observed titer following three primary injections of DTP given elsewhere, followed by DT booster [1]

Prebooster range antitoxin units	1	2	4	8	16	32	64	128	256	512	1,024	2,048	4,096	8,192	16,384	32,768	Total
0–<0.001:																	
Diphtheria													3				3
Tetanus															1		1
0.001–<0.01:																	
Diphtheria								2	2		2						6
Tetanus									2		1	4	1	1			9
0.01–<0.05:																	
Diphtheria					1	1		3									5
Tetanus					1				1	3							5
0.05–<0.2:																	
Diphtheria	1				2	3	7	1	2								16
Tetanus								3	5	1							9
0.2–<1.0:																	
Diphtheria			1		5	3											9
Tetanus			1		3	3	2	1									10
1.0–<5.0:																	
Diphtheria																	0
Tetanus	1			1													2
5.0–<10:																	
Diphtheria																	0
Tetanus			1														1
10–<20:																	
Diphtheria	1																1
Tetanus																	0
Totals:																	
Diphtheria	2		1		8	7	7	6	4		2		3				40
Tetanus	1		2	1	4	3	2	4	8	4	1	4	1	1	1		37

[1] DT, 0.2 ml. containing 2 Lf each of diphtheria and tetanus toxoids $AlPO_4$ adsorbed.

in subjects who had received a primary immunization with three doses of a multiple antigen.

Four subjects received only one primary dose of a multiple antigen (appendix C). Each responded vigorously to the booster dose, giving for diphtheria 20,000, 500, 130, and 42-fold rises, respectively. For tetanus the fold rises were 20,000, 1,200, 500, and 2. The 2-week postbooster titers were all indicative of adequate protection.

Table 4 presents fold increases for the group that received a primary course of three doses of DTP given by private physicians (appendix D). This group received a booster injection in 1949–50 and was therefore included in the study. The last recorded titers were actually postbooster titers rather than postprimary titers, as recorded for the other groups.

Diphtheria titers. Of the 40 subjects studied, all produced diphtheria antitoxin titers well above protective levels within a 2-week period. The response to a booster dose appears similar to that of subjects presented in tables 2 and 3.

Tetanus titers. Of the 37 subjects studied, all produced tetanus antitoxin titers well above protective levels within a 2-week period. The response to a booster dose was similar to that of subjects presented in tables 2 and 3.

Titer Changes After Booster

Because it was impossible to obtain all blood samples on schedule for each subject, those subjects were selected in whom all significant blood samples were tested. The only samples missed in this selected group were the 2-month and 24-month samples on some individuals.

Table 5 presents the frequency distribution

Table 5. Frequency distribution and geometric mean titers at prebooster [1] and successive postbooster [2] intervals

Titer range	Prebooster injection	Interval from booster					
		Weeks		Months			
		1	2	2	6	12	24
Total children	45	45	45	24	45	45	26
Diphtheria:							
<0.001	2						
0.001–<0.01	4						
0.01–<0.05	15					1	1
0.05–<0.2	12	1			5	7	4
0.2–<1	7	14	1	4	7	10	10
1–<5	5	21	14	13	23	24	8
5–<10		5	13	3	6	1	2
10–<20		2	14	4	4	2	1
20–<40		2	3				
40–<80							
80–<160							
Geometric mean	0. 06	1. 75	6. 32	1. 69	1. 69	0. 97	0. 73
Tetanus:							
<0.001							
0.001–<0.01	3						
0.01–<0.05	10						
0.05–<0.2	18						
0.2–<1	6	2				8	6
1–<5	7	12	2	6	22	18	10
5–<10		10	6	3	8	7	3
10–<20	1	8	10	6	4	4	6
20–<40		8	12	3	9	8	1
40–<80		5	10	6	2		
80–<160			5				
Geometric mean	0. 13	8. 39	24. 50	3. 86	6. 20	3. 72	2. 97

[1] Primary injections, DTP.
[2] Booster injection, DT.

Table 6. Distribution of children in study, according to interval between primary and booster injections of diphtheria and tetanus antigens, age, and sex

Interval between primary and booster injections, age, and sex	Diphtheria antigen		Tetanus antigen	
	Prebooster and 2 weeks	1 week	Prebooster and 2 weeks	1 week
6–9 year interval				
Age 4–6 years:				
Male	11	10	11	10
Female	15	12	14	11
Age 7–10 years:				
Male	11	11	9	9
Female	17	14	15	13
10–13 year interval				
Age 4–6 years:				
Male	18	17	16	15
Female	17	16	17	16
Age 7–10 years:				
Male	4	4	4	4
Female	5	5	5	5
Total	98	89	91	83

and geometric mean titers for 45 children studied consecutively for 12 months; 26 were studied for 24 months. Only 24 subjects were available for the 2-month titration and 26 for the 24-month titration. At the time of the booster injection the diphtheria antitoxin titers for six subjects were below 0.01 units per milliliter, the level generally accepted as protective; 15 had titers in the range of 0.01–0.05 units; and 24 had titers greater than 0.05 units. One week after booster all but one had a titer above 0.2 units, giving a geometric mean titer of 1.75 units. The maximum response, a geometric mean titer of 6.32 units, was observed at the end of the 2 weeks. At 24 months after the booster the geometric mean diphtheria titer was 0.73, considerably above the corresponding prebooster mean of 0.06. The minimum 24-month titer was 0.01–<0.05 units of antitoxin per milliliter of serum. Generally, the analysis of this group confirms the observations on the larger group, namely, that the response was, without exception, both rapid and marked.

The distribution of subjects with reference to prebooster tetanus antitoxin response by titer at each period is also presented in table 5. Three subjects had prebooster titers below 0.01 units, and 10 had a titer between 0.01 and 0.05 units. All others had a titer greater than 0.05 units. The geometric mean titer at the time of the booster injection was 0.13 units. One week after the booster the response was marked in all subjects; geometric mean titer, 8.39. The maximum response, geometric mean titer 24.50, was observed at the end of 2 weeks with subsequent decline to 2.97 at 24 months. The minimum titer at 24 months was in the 0.2–1.0 range.

In general, the rate and degree of response in the selected group of subjects followed the same general trend as for the entire group. At the end of 24 months the titers had not fallen to the prebooster levels.

Age, Sex, and Interval Between Injections

In this analysis all children were included from whom a prebooster and 2-week postbooster titer had been obtained. One-week postbooster titers were also analyzed for those on whom data were available. Total numbers in the analyses were:

	Diphtheria	*Tetanus*
Prebooster and 2-week titers	98	91
1-week titers also	89	83

Preliminary examination of the data suggested the possibility that children for whom the interval from primary inoculation to booster was longer had lower prebooster titers than observed in those for whom the primary-to-booster interval was shorter.

Since composition of the age-sex groups varied markedly with respect to the number of persons with shorter or longer primary-to-booster intervals, this factor was taken into account in the analysis and the children were classified into interval, age, and sex groups (table 6).

Geometric mean titers with 95 percent confidence limits were calculated for each group (table 7). The lower 95 percent confidence limits of the 1-week geometric mean diphtheria titers were above the 95 percent confidence limits of the prebooster levels in all groups except the males aged 7–10 years, who were given the booster 10–13 years after primary immuniza-

tion. In this group the lower confidence limit (0.40) of the 1-week titer was less than the upper confidence limit (1.9) of the corresponding prebooster titer. Since only four children were in this group the discrepancy does not seem important. At 2 weeks after the booster even this small group had a geometric mean titer significantly above its prebooster level.

Results with the tetanus antigen were similar in all respects. Although the data in table 7 indicate that age and sex are not factors of critical importance in response to the diphtheria and tetanus antigens, an appraisal of the extent to which response varies with these factors was carried out.

The procedure selected was an analysis of variance of log reciprocal titers before the booster inoculation and 2 weeks thereafter. Analysis in terms of the parameters of some functional relation between titer levels before and after the booster was rejected since examination of the data as presented in table 7 indicated that titer levels 1 or 2 weeks after the booster inoculation were largely independent of prebooster titers. The method chosen enables comparisons among the groups before and after the booster but does not predicate any mathematical relationship between the prebooster geometric mean titer for a particular group and its value after the booster inoculation.

The method of analysis is based on the assumption that the log reciprocal titer for a given individual includes additive components characteristic of an individual's age, sex, and interval from the primary to the booster inoculation.

Results of the various tests made may be summarized as follows:

Diphtheria titers. No significant differences by age, sex, or interval from primary to booster inoculation were found in either the prebooster titrations or in those at 2 weeks after the booster inoculation. Significant interactions were found at the prebooster titration but scrutiny of the data in detail did not indicate any unusual responses which might account for their presence.

Tetanus titers. A corresponding analysis of the tetanus data indicated no significant difference in titer associated with age or sex at either the prebooster titration or at titration 2 weeks after the booster inoculation. No evidence of interaction was found at either titration.

A significant difference was found in association with the interval from primary inoculation to booster inoculation. Before the booster inoculation children's serums titrated 6 to 9 years after the primary inoculation had a geometric mean titer of 0.246, whereas serums titrated 10 to 13 years after the primary had a geometric

Table 7. Geometric mean titers before and after booster inoculation of diphtheria and tetanus antigen, by interval between primary and booster injections, age, and sex

Time of titration and interval (years) between primary and booster injections	Age (years) at primary injection	Diphtheria antigen				Tetanus antigen			
		Number of persons		Geometric mean titer		Number of persons		Geometric mean titer	
		Male	Female	Male	Female	Male	Female	Male	Female
Prebooster:									
6–9	4– 6	11	15	0. 08	0. 02	11	14	0. 68	0. 11
	7–10	11	17	. 11	. 13	9	15	. 21	. 27
10–13	4– 6	18	17	. 05	. 09	16	17	. 06	. 05
	7–10	4	5	. 20	. 02	4	5	. 80	. 06
1 week postbooster:									
6–9	4– 6	10	12	3. 2	2. 0	10	11	17. 0	15. 5
	7–10	11	14	3. 1	2. 6	9	13	8. 0	10. 2
10–13	4– 6	17	16	1. 0	1. 6	15	16	6. 6	6. 5
	7–10	4	5	1. 3	. 88	4	5	7. 6	16. 5
2 weeks postbooster:									
6–9	4– 6	11	15	8. 2	5. 3	11	14	31. 9	29. 6
	7–10	11	17	8. 8	6. 5	9	15	24. 7	26. 4
10–13	4– 6	18	17	8. 8	7. 0	16	17	30. 0	19. 7
	7–10	4	5	8. 1	5. 0	4	5	17. 3	34. 4

mean titer of 0.071. At 2 weeks after the booster no significant difference was found between those with a shorter or longer interval from the primary to the booster inoculation.

Discussion

Of great significance, we believe, was the observation that the response to the booster injections of diphtheria and tetanus toxoids uniformly resulted in prompt and vigorous increases in circulating antitoxin levels in spite of the fact that 7 to 13 years had elapsed without intervening injections of these antigens.

The fact that each of our subjects responded to a booster injection so many years after primary immunization suggests that the present practice of giving a booster injection every 3 or 4 years may not be necessary. These results confirm many previous observations on the effectiveness of tetanus toxoid and certainly support the view that a booster dose of tetanus toxoid will be of incontestable value when a reliable history exists of primary immunization within 5 years or of primary plus reinforcing or booster doses at any time.

The use of reinforcing or booster doses may have value, particularly in children, against tetanus resulting from casual or unrecognized wounds since reinforcing or booster doses of tetanus toxoid may result in higher so-called resting titers of circulating antitoxin.

Even though routine booster injections every 3 or 4 years may not be indicated for either diphtheria or tetanus, they may remain desirable. The following circumstances would justify booster injections:

- Injury with risk of contracting tetanus.
- Abnormal prevalence or risk of exposure to diphtheria.
- Change of environment; for example, travel or, under certain circumstances, major change of school or residence.
- In the event of disasters, through crowding, dislocation, and so on.

The maximum response following booster injection was observed in approximately 2 weeks and all persons injected attained titers of 0.01 units or more of diphtheria and tetanus antitoxin within 1 week. Following the maximum response (2 weeks) the titers decreased gradually with time, but were still well above the prebooster levels 2 years later.

These observations raise several pertinent questions:

What happens to a person with resting titer when he is a temporary carrier or is exposed to a disease? Previous investigators have presented data strongly suggesting that such individuals get a booster response in the absence of clinical diphtheria infection but no definitive information on this point has come to our attention.

How necessary are frequent routine "boostings" and are there contraindications to frequent injections? For example, are frequent boosters creating hypersensitivity in a small proportion of individuals who have received numerous booster injections?

The tables provide substantial confirmation of the fact that a person who has had a primary series of inoculations of the antigens represented may be protected quickly through a booster injection in the face of exposure to disease even though his resting titer is low. Thus, the existence of a defense mechanism capable of quick response to restimulation may be of greater importance than actual resting titers, particularly since in this series the maximum titers attained were largely independent of prebooster titers.

The investigators will attempt to verify this point and measure the degree of antigenic stimulation following the actual exposure to infection of previously inoculated persons.

Summary

From the study of a group of 174 noninstitutionalized subjects who had received primary inoculation 7 to 13 years prevously it was found that rapid and vigorous increase in diphtheria and tetanus antitoxin levels followed a booster injection containing 2 Lf (Limes flocculation) units of diphtheria and tetanus antigens, aluminum phosphate adsorbed. Even in those few subjects who had received only one or two doses of antigen in their primary immunization, the response to the booster was rapid and adequate.

In all subjects tested both diphtheria and tetanus antitoxin titers were 0.01 units or more within 1 week following booster injection.

The highest titers observed occurred in 2 weeks after inoculation, followed by a slow decline through a 2-year period; however, titers did not return to prebooster levels during the 2-year period following booster doses.

A booster injection of 0.2 ml. of diphtheria and tetanus toxoid, aluminum phosphate adsorbed, and containing 2 Lf of each, produced no undesirable reactions in our group of subjects.

The significance of the resting titer must be further studied in its relationship to the existence of a "defense mechanism" for antigenic response.

Present policies of routine booster injection need to be re-evaluated in the light of the observations in the group of 174 subjects reported here.

It is safe to suggest that a booster injection should be given at the time of exposure to a particular disease, during the time of prevalence, and at the time of disaster. Routine boosters need not be given every 3 or 4 years and the time interval for routine practice may be considerably extended.

DOCUMENTATION NOTE

Appendix tables A–D, giving detailed data on response to booster injections of multiple antigens, have been deposited as document No. 6959 with the American Documentation Institute Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A photoprint may be obtained by remitting $2.50; a 35-mm. microfilm by remitting $1.75. Cite document number. Advance payment is required. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.

The appendix tables will also be included with reprints of the paper, which may be obtained from the authors.

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Metropolitan Health Training Course

A 2-week training course on urban planning for environmental health will be given April 2–13, 1962, at the Robert A. Taft Sanitary Engineering Center in Cincinnati, Ohio.

Public health and urban planning personnel from State and local agencies and Public Health Service personnel from headquarters and regional offices will attend.

The course will make use of the "Environmental Health Planning Guide" (PHS Publication No. 823), a recently published Public Health Service manual. As part of the training, actual field surveys will be made in a nearby city.

Future courses on the subject will be given at the center and in regional Public Health Service offices. Additional information is available from the Chief, Metropolitan Planning Training Section, Division of Environmental Engineering and Food Protection, Robert A Taft Sanitary Engineering Center, Cincinnati 26, Ohio, and Public Health Service regional offices.