THE DURATION OF IMMUNITY TO TETANUS*

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It has been well established that immunity to tetanus in man follows a series of injections with plain or alum-precipitated toxoid.[1, 2, 4, 7, 11, 15, 16, 28] Because this method has been in use but for a comparatively short time, the duration of immunity and the response to a single "booster" injection four or more years after the initial series appear to merit further study. This paper reviews the development and use of toxoid and reports the antitoxin level and response of individuals who had their last injection more than four years previously.

In 1924, Descombey[8] described the production of a tetanus toxoid by the technique of Ramon,[24, 25, 26, 27] and the next year Ramon published the first of a series of papers concerning its manufacture and possible use. This work stemmed from the development of a useful toxoid from diphtheria toxin. At first the tetanus toxoid was likewise prepared by the addition of formalin to the toxin. Later, precipitation of the toxoid by alum was found to increase the antitoxin response.[1]

The amount of circulating antitoxin necessary to protect man has been estimated by several investigators. By analogy with results obtained from experimental animals given tetanus infection following skin abrasions, Cowles[7] suggested that in man a fairly certain protection would be given by 0.1 to 0.2 of a unit per cubic centimeter of serum. Bergey and Etris[2] set the minimum amount of antitoxin in serum at 0.1 unit, which is the antitoxin level four days after the administration of 1500 units of antitoxin.[9] Since the publication of these figures, other investigators have used them in discussing their results.

Bergey,[1] in 1934, suggested that immunization might be carried out by two injections of 1 cc. of toxoid, the second being given three months after the first. A third injection of 1 cc. was to be given following injury. The result of such a procedure, as shown by data obtained by Bergey and Etris[2] from thirty individuals, was that the levels of antitoxin reached in the sera were low in comparison to results obtained when injections

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were given more frequently.[3] In France and in pediatric medicine in this country, tetanus toxoid has been combined with diphtheria toxoid with some success.[12, 28]

Active immunization against tetanus for members of the armed forces was suggested by Sneath[29] and others before the outbreak of the second World War. The procedure used by the United States Army during the war underwent some modification as the result of further investigation.[17] The original plan called for the immunization of every soldier at the time of induction, with three injections one week apart, a single injection every year, a single injection before going to a combat area (if the individual had not been given a booster dose within the previous six months), and a single injection on injury. By the conclusion of the war only the initial series and the single injection on injury were given in some cases, though considerable variation in routine took place. In the British Army the routine differed in that initial immunization until 1941 consisted of two injections, because of the shortage of toxoid.[4] Instead of using toxoid at the time of injury, 3000 units of antitoxin were injected. Later the initial series was increased to three injections of 1 cc. each, but the use of antitoxin instead of toxoid was maintained.

The results of these procedures in the British and in the American Armies have been published by Boyd[4] and by Long.[17] Of the twelve cases of tetanus known to have developed in the Army of the United States, half of the men had not been given the basic immunization. Of the six which had no kind of immunization there were two fatalities. One of the two which had been given the basic but not the injury injection terminated fatally, as did two of the four cases which had both the basic and the injury injections. Of the 103 cases of tetanus collected by Boyd from reports of the British Army in the European and African campaigns, twenty-two (eleven fatalities) were considered to have been adequately protected, sixty-two (twenty-nine fatalities) were considered unprotected, and nineteen (eight fatalities) were doubtful or incomplete. No deaths are known to have occurred in those receiving two initial injections plus two or more annual booster doses.

Complications to the injection of toxoid in the Army of the United States were placed in two main categories by Long.[17] The first type was similar to the soreness at the site of injection, headache, general malaise, occasional chills, and fever after typhoid inoculation. The second type of reaction was characterized by the early appearance, usually within thirty minutes after the injection, of flushing and itching of the skin, perhaps urticarial eruptions, occasional edema of the lips and eyelids,

and, rarely, edema of the glottis and respiratory difficulty. These complications were decreased markedly, from 63 per 100,000 or less, by using toxoids that did not contain Witte's or Berna's peptone.[6, 19] Complications to injection of toxoid are not reported by Boyd, but similar circumstances seem to have prevailed.[5, 20, 30] Clearly, these difficulties are small in comparison to the dangers and time sometimes involved in the administration of antitoxin.

That an adequate rise in titer follows a booster injection of toxoid three years after basic immunization has been shown by several investigators.[4, 18, 23] For longer periods of time, fewer data have been published. Long[17] finds that the response is adequate for both the three- to four-year period and the four- to five-year period. The seven cases he reports show an adequate response in seven days, but the questions might well be asked whether this is a large enough sample and whether a shorter period might not more nearly represent the circumstances for which a rise in titer might be necessary in time of injury. Hence the present work was undertaken.

Method

The titrations of antitoxin level reported in this paper were carried out by a method which utilizes mice.[13, 14] A 20-gm. mouse was injected subcutaneously with a solution containing 0.5 cc. of the serum of the individual being tested and 0.5 cc. of toxin (Lederle), diluted to the appropriate strength, which had been mixed and allowed to stand for thirty minutes. The toxin was prepared by making a stock solution of 200 mg. of tetanus toxin (the test dose being 0.00004 gm. per 0.5 ml. equals 0.1 unit) in 50 cc. of glycerol. Dilutions from stock were made with broth. The strengths used were 1.0 unit (1 cc. of stock plus 9 cc. of broth), 3.16 units (1 cc. of stock plus 2.16 cc. of broth), and 0.01 unit, 0.0316 unit, and 0.316 unit prepared in a similar manner. Death of the mouse within four days was considered a positive test. An individual whose serum protected mice at a level of 0.0316, 0.1, and 0.316 but not at 1.0 and 3.0 units, as evidenced by the fact that the mice died within four days in only the latter two cases, is reported as having a level of 0.316 unit of tetanus antitoxin. The serums, many of which were obtained by the Department of Health of Yale University, were drawn immediately before a booster dose of 0.5 cc. of alum-precipitated toxoid was administered. Six subjects were tested at five and at seven days, and the serums of the remaining seventeen individuals were obtained at five days only. All of the individuals studied were males in the 20 to 30 age group who had served in the armed forces.

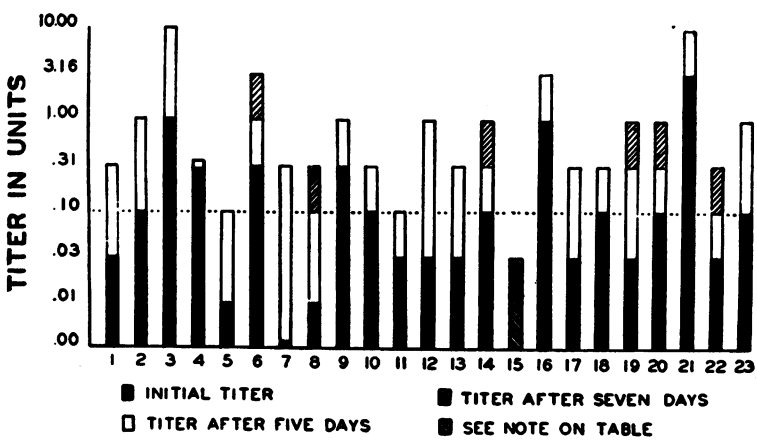
Results

Considerable variation was found in the sera tested. In every case the sera were found to have at least 0.1 unit of antitoxin five days after

SUMMARY OF RESULTS—IMMUNITY TO TETANUS

Subject No.	*Elapsed time between basic immunization and present titration*		*Elapsed time between last booster dose and present titration*		*Initial level*	*After 5 days*	*After 7 days*
	Years	*Months*	*Years*	*Months*			
1	3	10	—		.0316	.316	—
2	5	0	3	11	.1	1.0	—
3	5	0	3	11	1.0	10.0	—
4	5	0	4	0	.316	.316	—
5	4	1	—		.01	.1	—
6	4	1	—		.316	1.0	3.16
7	5	3	5	0	—	.316	—
8	4	2	—		.01	.1	.316
9	4	3	—		.316	1.0	—
10	4	4	—		.1	.316	—
11	5	11	4	7	.0316	.1	—
12	4	8	—		.0316	1.0	—
13	4	8	—		.0316	.316	—
14	4	10	—		.1	.316	1.0
15	5	0*			—	.0316	—
16	5	0	—		1.0	3.16	—
17	5	1	—		.0316	.316	—
18	5	1	—		.1	.316	—
19	5	1	—		.0316	.316	1.
20	5	2	—		.1	.316	1.
21	7	4	5	2	3.16	10.0	—
22	5	4	—		.0316	.1	.316
23	6	2	—		.1	1.0	—

*After titrations had been completed, investigation of previous inoculations showed that only one initial toxoid injection 5 years before test and perhaps one more injection 4 11/12 years before test had been given.



the booster injection. The six serums tested at seven days showed a continuance of the rise. In the one case where no residual titer was found and the response was 0.0316 unit, closer investigation showed that the initial immunization had not been adequate. Nine others did not show the level considered as a minimum for protection before the booster was given. See Table and Chart.

Comment

Before considering the duration of the immunity produced by tetanus toxoid, it may be pointed out that considerable variation in the protective qualities of the various market preparations has been described.[10] Administration of the toxoid in individuals 4, 5, and perhaps 6 years after initial immunization or after the last booster appears to give adequate protection in five days, using as a minimum standard 0.1 unit. How adequate this level may be, since it is a value obtained only on indirect evidence, remains speculative at this time. No differences in response because of sex were noted by Peshkin;[23] no mention of such differences was found in reviewing the literature. Peshkin noted that in children the titer was higher and more lasting when a booster shot was given four years after initial immunization than it was when this stimulus was given three to fifteen months after the basic injection.

In cases where increased toxin production seems likely because of the nature of the wound, a booster given immediately after injury might not be sufficient. While the data reported in this paper would seem to indicate, as do the reports of Long and Sartwell[17] and of Peshkin,[21, 22, 23] that the booster stimulation of antitoxin may be adequate for a longer period of time than is generally recognized, statistical analysis of the relatively small amount of data thus far reported is not rewarding.

Conclusion

Twenty-three individuals who were given basic tetanus immunization with toxoid or who were given their last booster four or more years ago were tested before and five days after an injection of 0.5 cc. alum-precipitated toxoid. Six were also tested at seven days. Results indicate that by present standards an adequate antitoxin response developed within five days after injection.

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