ON THE PERMANENCE OF ANTI-TETANUS IMMUNIZATION*

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THE PREVENTION OF tetanus has long concerned those responsible for the care of injuries. The ubiquity of *Cl. tetani*, its requirement of anaerobic conditions for growth and for the production of toxin, the clinical course of the infection and its high mortality in spite of modern therapeutic methods, are well known. Since World War I, based on conclusions drawn from the experience of the British Army, it has been assumed that a single injection of tetanus antitoxin, given shortly after an injury was incurred, resulted in a high degree of protection against tetanus. The use of a prophylactic injection of 1500 units of antitoxin became, and is accepted, common practice. The horse has been the standard source of antitoxin and, therefore, the phenomena resulting from the injection of foreign protein have been of frequent occurrence, varying from mild sensitivity with urticaria to anaphylaxis and death. Whether to administer antitoxin and accept the consequences resulting from the injection of horse serum, or whether to withhold antitoxin and accept the more remote chance of having the patient suffer from tetanus is a dilemma faced daily by surgeons.

Since 1940, however, an increasing portion of the population of the United States has been actively immunized against tetanus toxin. This group, now coming to include all members of the Armed Forces, all veterans of the Armed Forces who served in or subsequent to World War II, and in many communities all children, may amount to 20 million, and constitutes a major health asset. As will be shown below, there may be some question as to the value of the presently accepted method of tetanus prophylaxis, using antitoxin. There is no question, however, of the value of active immunization. The experience of the United States Army (which included the Air Force at that time) in World War II stands as adequate proof of the latter. Long and Sartwell[2] were able to find only 12 cases of tetanus among 2,734,819 admissions to hospitals for wounds and injuries. There were five fatalities, but only *one* of the deaths occurred in a soldier who had been properly immunized and who had received a stimulating dose of toxoid subsequent to his basic immunization. When it is pointed out that tetanus usually occurs after a trivial injury and, further, that the number of such injuries treated by battalion medical officers plus those which were untreated must have run into several millions more, it is obvious that the incidence of tetanus was exceedingly low, and that the protection afforded was as nearly perfect as anything biological can be.

In Baltimore, prior to 1940, a number of pediatricians began the practice of routinely immunizing infants and pre-school children, using combined diphtheria and tetanus toxoid. This practice has been continued and extended; in 1950, the Baltimore City Health Department adopted this practice in its well-baby clinics. It has also become

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routine to immunize the medical students of The Johns Hopkins University and the students of The Johns Hopkins Hospital School of Nursing. This has meant that an increasing proportion of the patients treated for injuries by the staff of the hospital were individuals who had already been actively immunized against tetanus toxin. The question arose continually as to whether an individual so immunized in the past needed a booster dose of toxoid or an injection of antitoxin, if the interval since immunization was more than a few months. Various arbitrary routines were followed, but, until recently, no factual data existed upon which a sound procedure could be based. This lack of knowledge led to the present study, for it seemed that tetanus antitoxin was being administered more often than was necessary or desirable.

TABLE I. *Clinical Tetanus in Baltimore 1928–53.*

At initial injury	Patients	Deaths
No antitoxin	142	71
Received antitoxin	25	13

Antitoxin levels in the serum of 175 individuals were determined by a standard method.[5] For purposes of comparison, the subjects studied were divided into three groups: first, a group of 72 men and women who had served with the Armed Forces of the United States or of the British Commonwealth during World War II and whose last tetanus toxoid inoculation had been at least five years previous to this study; second, a group of 73 individuals who had received tetanus toxoid within the past five years; and third, a group of 30 individuals who had never served in the Armed Forces nor received an injection of tetanus toxoid. Initial determinations were made, each subject was then given 0.5 ml. of fluid tetanus toxoid intramuscularly, and subsequently blood samples were taken at intervals up to 14 days in most instances.

In Figure 1 (upper portion) are shown the results of the initial serum antitoxin levels of individuals whose last previous injection of tetanus toxoid was from five to 11 years before. It will be noted that every member of this group had a measurable level, and that 75 per cent of the group had serum levels of 0.05 units per ml. or higher. It has been generally accepted, since World War I, that a serum level of 0.1 units per ml. of antitoxin constituted a protective level. This was based on determinations made after passive immunization. If this assumption is correct, it is apparent that most of the subjects in this first group have maintained a protective level of serum antitoxin despite intervals of five to 11 years since their last booster injection.

The results of the initial determinations made from the blood of those individuals who had toxoid injections less than five years previously are shown in the lower part of Figure 1. The distribution pattern is about the same as in the first group, but it is seen that the second group has a generally higher level than the first; 93 per cent of the second group had levels of 0.05 units per ml. or higher, and the median level of this group is about ten-fold that of the first.

As could have been predicted, no detectable level of tetanus antitoxin was demonstrable in the serum of any of the 30 individuals of group three. This group of subjects served as a control in two ways; first, as a check on the method of quantitating serum antitoxin, and second, as a control group in the study of the effects of one injection of tetanus toxoid.

The results of serum antitoxin determinations following the administration of a booster dose of 0.5 ml. of fluid tetanus toxoid to individuals of the first group are shown in Figure 2. Within seven days, there was a rapid and large rise in the serum antitoxin level, and at 14 days nearly all individuals reached a level of 10 units per ml. at least. Determinations of higher levels than 10 units per ml. were not made. Especially noticeable was the hundred-fold

or more rise in the serum antitoxin levels of those subjects whose initial determination was 0.01 units per ml. or less. Intermediate determinations indicated that the rise in level began about the fourth or fifth day after the booster dose was given.

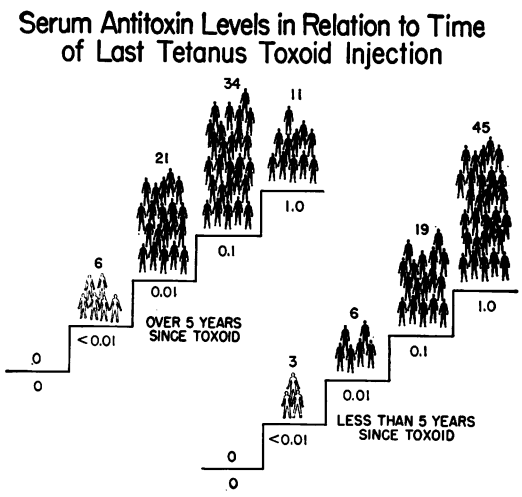

FIG. 1.

By way of contrast, no antitoxin could be demonstrated in the blood of 15 individuals who had never had tetanus toxoid previously, even at 14 days after an initial dose was given.

Previously published studies[1, 4] have described the pattern of serum antitoxin levels in individuals following the intramuscular injection of 1500 units of tetanus antitoxin. The usual levels were 0.1 units per ml. at 24 hours, 0.15 to 0.25 units at four days, and back down to 0.1 units at seven days. Thus, it can be argued that the four-day period necessary for the production of serum antitoxin in the immunized individual who is given a booster dose is no longer than the period necessary to reach peak levels in passive immunization. Moreover, the elimination of serum antitoxin occurs more rapidly in passively immunized individuals who exhibit sensitivity phenomena.

Anyone who has treated patients for clinical tetanus infection knows the therapeutic value of antitoxin. There is some reasonable doubt, however, as to the prophylactic value of one injection of 1500 units of tetanus antitoxin. On purely theoretical grounds, one might wonder how such a small and evanescent amount of antitoxin could afford much protection. The antitoxin would, no doubt, neutralize equal amounts of toxin which might be produced by *Cl. tetani* growing in the patient, but what if the organisms continue to grow and produce? Until now, the chief basis for assuming that an injection of tetanus antitoxin exerts a prophylactic effect has been the reported experience of the British Army in World War I. An initial rather high incidence of tetanus among the British wounded at the outset of that war fell to a lower figure after the innovation of routine antitoxin injections, but the amount used was only 500 units at that time.[3] One wonders if the switch to débridement and open treatment of battle wounds from a closure method, made at about the same time, might not have been a more important factor.

In the hope of shedding some light on this problem, a review was undertaken of the case histories of all patients treated for clinical tetanus in the general hospitals of Baltimore during the past 25 years. A search of the records of the 16 general hospitals which were in continuous operation during the years 1929 to 1953 produced records of 169 cases of clinical tetanus infection. Admittedly, the diagnosis may not always have been correct, nor all of the cases discovered, and it is conceded at once that it would be unwise to draw far-reaching conclusions from such data. Table I shows the results of this survey. It will be noted that clinical tetanus does develop despite the prophylactic use of tetanus antitoxin, and that the mortality rate is just as high as in the patients who did not receive prophylactic antitoxin.

In the great majority of the patients who had tetanus, the initial injury was of the classical variety, a puncture wound of the sole of the foot, a splinter, or the wound from a blank cartridge or cap. The records

show that the majority of these patients had what they considered to be trivial injuries, and that they did not seek medical care. In view of the vast number of such injuries which must occur annually in a metropolitan area of about a million and a half inhabitants, it is significant that only seven individuals develop clinical tetanus each year, on the average, and that one of the seven is a patient who has received prophylactic tetanus antitoxin. Tetanus is thus a very uncommon complication of trivial injuries, and it is a temptation to wonder about the *prophylactic* value of antitoxin. One suspects that many fewer splinters and trivial puncture wounds are treated in hospital emergency rooms or doctors' offices than are treated by home remedies or simply ignored.

The 25 patients who developed tetanus despite being given prophylactic tetanus antitoxin, with 13 fatalities, are offered as evidence suggesting that the growth of the *Cl. tetani* and production by them of toxin continued after the horse serum antitoxin was excreted and/or neutralized. In these patients, there would seem to have been no growth-inhibitor effect of the antitoxin on the clostridia. An agent which did have such an effect would be a more logical one for prophylaxis, and studies are being undertaken in this direction. The occurrence of fatal tetanus, even though a prophylactic injection of antitoxin was given, has been reported before,[6] but the significance of the matter may have been misinterpreted. If the antitoxin were truly a prophylactic agent, there should be a lowered attack rate and a more benign form of the disease in those attacked; neither of these can be shown to occur, it would seem.

It is of interest that tetanus was observed during this period in only two individuals who had been actively immunized. In both, the symptoms were of brief duration; recovery occurred in one without any therapy and, in the other, following administration of one dose of antitoxin. While it is likely that the occurrence of infection with *Cl. tetani* would serve as a sufficient stimulus to call out antitoxin in some immunized individuals, and although it has been shown in this study that a booster dose of toxoid will bring out a response in four or five days,

Effects of Tetanus Toxoid Injection in Individuals Whose Last Previous Injection Was 5 Years or More Ago

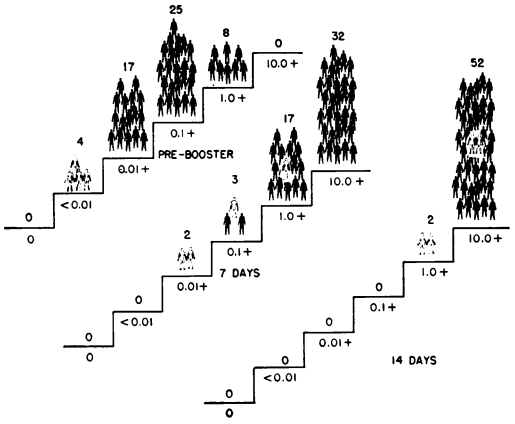

FIG. 2.

it is obvious that an occasional immunized individual, who suffers from an initially overwhelming infection, will develop tetanus. Such a patient will need antitoxin. If such a patient should be sensitive to horse serum, preliminary studies[5] indicate that the blood and serum of previously immunized human donors are valuable sources of effective antitoxin.

Finally, some consideration must be given to the very practical and every-day problem of identifying those patients who are immunized. With regard to children, the parents must be able to furnish reliable information before it is safe to assume that a given child has been immunized. Adults who have served in the Armed Forces since 1941 are carefully questioned, and, if they can recall receiving a course of injections, it is assumed that they have been immunized. It is apparent, nevertheless, that there is room for error. Tattooing has been suggested as a means of permanent identifica-

tion of various significant medical data, but is probably not practical. Anyone with Army experiences knows, also, the problems and unreliability of such methods as dog-tags or immunization registers. The majority of citizens, however, can be relied upon to know who they are, and it is suggested that one practical way of handling this problem would be to maintain a central indexed file of names in the health department of each community. A phone call might thus establish the immunity data with certainty, even in the case of a transient patient.

SUMMARY AND RECOMMENDATIONS

In recent years, an increasing portion of the population of the United States has been actively immunized against tetanus toxin. The present study indicates that actively immunized individuals continue to have measurable levels of serum tetanus antitoxin up to 11 years, and retain during this period the ability to produce high levels of serum antitoxin, rapidly, in response to a booster injection of toxoid. It is recommended, therefore, that in civilian practice a stimulating dose of tetanus toxoid alone be administered when indicated for the prophylaxis of tetanus in the treatment of injuries sustained by individuals known to have had active service in the Armed Forces of the United States during or subsequent to World War II. The same practice is recommended for other individuals, both children and adults, when there is a reliable history of previous active tetanus immunization. Effort should be made to continuously enlarge the portion of the population enjoying basic immunity to tetanus. The suggestion is made that local health departments consider the establishment of a permanent immunization roster. A question as to the actual value of the prophylactic injection of tetanus antitoxin has been raised, and it is hoped that this matter will be studied further.

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DISCUSSION.—DR. HARRIS B. SHUMACKER, JR., Indianapolis, Indiana: I want to congratulate Dr. Stafford, Dr. Turner and Dr. Goldman on the investigation they have reported today. I believe it is of the utmost importance. Perhaps my chief qualification for discussing this paper is the fact that I may be the best-immunized person against tetanus alive today. About 16 years ago, through the influence of the late Dr. Abel, a number of us at the Department of Surgery at Hopkins were stimulated to carry out some investigations concerning the pathogenesis and treatment of tetanus. Since we were using potent toxins, we were desirous of protecting ourselves as much as possible; and, not understanding as well as we do today the immunity that is conferred by the procedure which I believe Ramon introduced as long ago as 30 years, we immunized ourselves quite regularly and frequently. I am quite certain that our titers must have risen to fabulous levels.

The value of this method of immunization mentioned, has been demonstrated without question in the most clear-cut manner by the experiences in warfare between the Japanese and Chinese before World War II, during World War II and during the Korean conflict. The problem that has remained with us, and which I think Dr. Stafford and his associates have settled now, concerns how long this immunity persists, and how long individuals so immunized retain a responsiveness to a re-injection of