UNEXPECTED RESPONSES OF ACTIVELY IMMUNIZED MEN TO A BOOSTING DOSE OF TETANUS TOXOID

BY

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and

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Little work has been done to determine the effect of successive injections of tetanus toxoid in individual persons. In a study of a small group of adults actively immunized with tetanus toxoid, Evans (1943) found that in no instance was the antitoxin titre eighteen months after the third injection lower than it was four months after the second; in four of eleven persons it was definitely higher. The second injection was given nine weeks after the first, and the third injection ten months after the second.

During a recent investigation into methods for the prevention of clinical tetanus, we have been able to study the effect of boosting doses on men who had received varying numbers of injections of tetanus toxoid previously. Some results have already been reported and are in course of publication in the Proceedings of the Royal Society of Medicine (Sachs, 1952). The work recorded here was not reported owing to shortage of time, and appears to us to be of sufficient interest and importance to justify the publication of a short note. The results of the complete investigation will be published in the near future.

This part of the investigation was designed to determine the effect of a boosting dose of toxoid injected either alone or at the same time as 500 units of tetanus antitoxin given in a different site. The volunteers concerned were bled before and at certain fixed times after injection, a few being bled as late as six months after injection so that an idea of the duration of immunity could be obtained from measurement of the antitoxin titre at this time. It should be mentioned that the six-month blood sample was obtained from these particular men because it was anticipated from their earlier responses to the injection, that information of practical importance would be obtained thereby. They do not therefore constitute a random sample. All the men received the boosting dose, with or without an injection of tetanus antitoxin, during the months of February, March or April, 1951.

Table I shows the antitoxin titres of these men at the time of injection, ten to twelve days, two months and approximately six months later: the titres are correct to approximately ±10 per cent. The men are divided into three groups: those in Group A received their first boosting dose in this investigation, those in...
Group B had previously received one, and all in Group C had received two or more boosting doses previously. The first boosting dose is here defined as the third injection of the initial course of immunization, given six to twelve months after the second dose.

The table shows that all the men in Group A had higher titres six months after injection than they had at the time when the injection was given. The first man (3/4) was judged by his pre-injection titre to be a good responder, for he had some circulating antitoxin present twelve years after the second injection of the initial course. Six months after the boosting injection his antitoxin titre was higher than those of three of the four men who received the third injection within fifteen months of the second. These three men appeared, however, to be poor responders to immunization, for they had no detectable circulating antitoxin at the time of their third injection. The fourth man, 1/13, is clearly a good responder to immunization with tetanus toxoid.

In Group B both men showed relatively high titres ten days after the injection of toxoid, but the losses occurring between the second and sixth month showed a marked contrast. These men had somewhat similar immunization histories, but the figures in the table suggest that 8/11 might continue to show a fairly rapid loss after the sixth month, while the rate of loss in 8/13 had already shown an appreciable slowing down. Their six-month titres were the highest of any recorded in the table.

It is, however, Group C that provides the result of greatest importance. The three men in this group had all received two or more boosting doses prior to the injection given in this investigation. It will be noted that the titres six months after injection were very little different from those recorded before injection. In

### Table I.—The Response of Actively Immunized Men to a Boosting Dose of Tetanus Toxoid Injected During February—April, 1951

<table>
<thead>
<tr>
<th>Immunization Dates</th>
<th>Antitoxin Titre (Units/ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First two Injections</td>
</tr>
<tr>
<td>Man</td>
<td>Group</td>
</tr>
<tr>
<td>3/4</td>
<td>A</td>
</tr>
<tr>
<td>1/11</td>
<td>A</td>
</tr>
<tr>
<td>3/2</td>
<td>A</td>
</tr>
<tr>
<td>8/7</td>
<td>A</td>
</tr>
<tr>
<td>1/13</td>
<td>A</td>
</tr>
<tr>
<td>8/11</td>
<td>B</td>
</tr>
<tr>
<td>8/13</td>
<td>B</td>
</tr>
<tr>
<td>1/1</td>
<td>C</td>
</tr>
<tr>
<td>4/3</td>
<td>C</td>
</tr>
</tbody>
</table>
Unexpected Responses to Tetanus Toxoid

1/1, the six-month titre was slightly higher than that before injection, in 4/3 it was the same within the limits of error, and in 8/1 it was definitely lower.

It is a matter of some importance that a boosting dose of toxoid can confer little or no benefit as judged by the antitoxin titre six months later and that an adverse effect can be produced in some persons. Greenberg (personal communication) agrees that in certain circumstances an injection of prophylactic may be harmful.

The histories of these men will be considered briefly. The second man (4/3) had received two boosting injections in 1950; the second of these was administered six months before the dose given in this investigation. It is therefore possible that appreciable loss of antitoxin was still occurring, and we can only conclude that had he not received a boosting dose, his antitoxin titre might have fallen further.

In the case of 8/1, who received tetanus toxoid and antitoxin in different sites, the early response to the boosting dose of tetanus toxoid was interfered with; it was thought that crowding-out occurred because of a rapid production of precipitin in response to the injection of horse antitoxin-protein, to which he had some immunity as a result of a previous injection. His response to injection will be considered fully in the report presenting the complete results; this was the only case in which such interference occurred. It is disturbing to note that his antitoxin titre six months after active-passive immunization was appreciably lower than that found nine months after the previous boosting dose given in 1950. If this result is in any way attributable to the antigenic effect of the injection of heterologous antitoxin-protein, a similar result might be expected to occur in some persons injected with a combined prophylactic, if they had marked basal immunity to one component: a suppression of the response to other components might also occur.

The case of 1/1 is, however, the most disturbing. There is no reason to doubt the accuracy of the immunization history: he had received no injections of tetanus toxoid for about six years. The titre measured at the time of injection in this investigation (0.7 unit per ml.) must therefore have been almost stationary. A very high level of antitoxin (32 units per ml.) was found ten days after injection, and a very considerable fall occurred thereafter, so that the titre found six months after injection (0.9 units per ml.) was hardly higher than that existing before the injection was given. The magnitude of the loss that occurred between the second and sixth month after injection suggests that further loss might continue at a considerable rate, so that his titre might fall below the steady level present before injection.

It should be remembered that these volunteers were specially selected and that this unfavourable result may be uncommon. It is also possible that the next injection received by these men may raise the permanent level of circulating antitoxin eventually reached to a higher level once again. It is, however, also possible that harm might be done by repeated injections of prophylactic after a certain level of immunity had been attained, unless larger doses were given. More work could profitably be done on this subject, for the possibility, however
remote, of a progressive lowering of the level of immunity after successive
boosting doses, is of paramount importance when considering reinforcing doses
of an immunizing agent.

It is also of interest to note the great contrast between the six-month
titres of men who had reached high ten-day values. One of these (8/13) had 27
units per ml. ten days after injection, and showed a fall only to 13 units per ml. at
six months; 1/1, however, who had 32 units per ml. ten days after injection,
dropped in titre to 0.90 units per ml. after six months. This result shows clearly
that the titre at the peak of the response may give no indication of the titre at a
later stage, and does not therefore provide reliable information of the duration of
immunity.

REFERENCES


Matters of Interest

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