and for the regulating of the time of return to work accordingly. And it should be added that the new suggestions as to the danger of certain minutely fragmenting fibrous silicates, on which stress has been laid by W. R. Jones (1933), serves to emphasize the importance of a careful scrutiny of the stone dusts so successfully used for "stone dusting" as a precaution against explosions. It may well be that the importance given, in the past, to the presence or absence of "free silica" may have blinded us to the existence of other dangerous elements capable, equally with or in greater degree than free silica itself, of producing silicosis.

PERSISTENCE OF TETANUS ANTITOXIN IN MAN FOLLOWING ACTIVE IMMUNIZATION

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During the past two years we have determined the antitoxin content in the blood serum of a group of adults at various intervals after subcutaneous injections of tetanus toxoid. From the beginning of this study subjects 1 to 16 have been given tetanus toxoid, supplied through the kindness of the Pasteur Institute, Paris, and subjects 17 to 29 have been injected with a similar toxoid, prepared at the Connaught Laboratories, University of Toronto.

Persistence of Antitoxin Two Years after Three Doses of Tetanus Toxoid

Serum was obtained from thirteen persons about two years after the last dose of the primary series of injections of tetanus toxoid. Of twelve persons in whom comparison was possible, as may be noted by Table I, the residual

TABLE I.—*Tetanus Antitoxin Response to the Injection of
Tetanus Toxoid*

Subject Number	Following Primary Series			Following Fourth Dose	
	Maximum Response	After 12-15 Months	After 2 Years	After 1 Week	After 1 Month
Units per c.cm. of Serum					
1	0.1	0.01	0.01	5.0	2.5
3	>0.1	>0.01 <0.01	0.025	1.25	2.5
4	>0.1 <0.5	>0.1 <1.0	0.25	5.0	—
7	>0.1	—	0.05	>5.0 <10.0	>5.0 <10.0
9	>0.1	>0.01 <0.1	0.1	2.5	2.5
10	0.25	0.01	0.01	>0.1 <0.5	>5.0
13	>0.25 <0.5	>0.01 <0.1	>0.125 <0.25	—	—
15	0.1	>0.01 <0.1	0.05	5.0	10.0
18	>0.1 <0.25	>0.01 <0.1	0.025	2.5	>2.5 <5.0
20	0.01	>0.001 <0.01	>0.01 <0.05	>1.25 <2.5	>1.25 <2.5
21	0.005	<0.001	<0.001	0.01	0.025
25	>0.01 <0.1	>0.01 <0.25	0.025	1.25	>1.0 <2.5
29	0.25	>0.01 <0.1	0.025	5.0	>2.5 <5.0

The symbols > and < represent "more than" and "less than" respectively

antitoxin showed no evidence of having fallen below that shown twelve to fifteen months after the last dose. Three of the group (subjects 4, 9, and 13) retained at least 0.1

unit of tetanus antitoxin per c.cm. In view of the limitation to accurate interpretation of the tests, the apparent increases in antitoxin titre shown by three of the group (subjects 3, 9, and 20) during the second year cannot be accepted without reserve. If subclinical infection by *Cl. tetani* were a possible explanation of such a delayed antitoxin increase, acting in this instance as a *secondary* stimulus, it is probable, as may be observed later in this paper, that a higher residual titre would be found than is shown here. It is therefore considered that the apparent increase in antitoxin titre over this period is probably not significant.

Antitoxin Response to Reinjection of Tetanus Toxoid after Two Years' Interval

A fourth dose of toxoid was given to the same group of twelve persons who had been given an initial series of three doses two years previously, and serum was obtained at intervals of a week and a month thereafter. Within a week an increase in antitoxin titre occurred in the order of ten to five hundred times more than the residual level shown two years after the primary series. After a month five (subjects 3, 10, 15, 18, and 21) showed a further increase in antitoxin titre, four showed no appreciable change, two showed a definite fall, and one serum was not tested. The most striking feature of the response is the fact that eleven persons developed tetanus antitoxin in amounts of between 0.1 and 10 units per c.cm. Subject 21, whose titre did not rise above 0.025 unit, has shown a poor antitoxin response throughout. Nevertheless, the increase shown here is similar in trend to that of the other members of the group. The rapid increase of antitoxin titre and the fact that after a month the antitoxin level so induced does not rapidly fall confirm our previously recorded observations.

Persistence of Antitoxin One Year after Reinjection of Tetanus Toxoid

A fourth subcutaneous dose of 1 c.cm. of tetanus toxoid given to fourteen persons about a year after a primary series of three doses has been shown to occasion a rapid increase of antitoxin within a week, thirteen of the group attaining or exceeding an antitoxin titre of 0.1 to 0.25 unit per c.cm., which level was maintained after a month.¹ A year later the sera of ten of this group (Table II) were available. One (subject 5) had retained approximately the same antitoxin titre as was found a month after the fourth dose, whereas in the others the titre had definitely fallen. Nine persons retained antitoxin in amounts varying from 0.1 to 0.75 unit per c.cm., these residual levels in general being substantially in excess of those found a year after the initial doses.

Comment

It is recognized that the development of antitoxin and an immunity to diphtheria may follow subclinical infection with the diphtheria bacillus. Should the presence of *Cl. tetani* in the human digestive tract as shown by Bauer² be capable of inducing a similar immunity to tetanus in men as has been shown by Tenbroeck³ in experimental animals, it would be expected that active immunity so acquired might be indicated by the presence of measurable amounts of antitoxin in the serum. There is no convincing evidence in the sera of sixty-five normal adults which have been investigated that would indicate the prevalence of this type of immunity in Toronto. However, it is possible to induce the development of tetanus antitoxin by the subcutaneous injection of tetanus toxoid, but as yet it is not possible to state definitely at what level this antitoxin must be maintained in the blood stream to confer immunity upon human beings.

The level of 0.1 to 0.25 unit per c.cm. of serum has thus been arbitrarily chosen as a criterion, because it represents, in our experience, the maximum antitoxin level reached in the blood serum of persons who were injected with 1,500 American units of tetanus antitoxin.⁴ Although this may be in excess of the level necessary to protect man from the development of clinical tetanus, we are as yet unable to suggest a standard of any greater merit. An initial series of three doses of tetanus toxoid has been shown to induce the development of tetanus antitoxin to the level of at least 0.1 unit per c.cm. in twenty-eight of a group of twenty-nine persons.⁵ Twelve to fifteen months later only three of these retained antitoxin at that level. Two years after the initial doses the sera of thirteen of these persons showed no evidence of a further loss in antitoxin titre, three retaining a level of 0.1 unit per c.cm. or more. This indicates that in general the fall in level is most rapid during the first twelve to fifteen months after the last dose of toxoid, following which the rate of loss in antitoxin titre is apparently much less.

It has been possible to show a marked response to the so-called *secondary* stimulus with tetanus toxoid in a group of fourteen persons a year after the initial series of doses.¹ A similar type of response is to be observed in this report when, with an interval of two years between the earlier series of doses and the further injection of a single dose of toxoid, much higher antitoxin levels are found within a week than were observed at any other previous period. Furthermore, this state persists for at least a month. Within a week of the last dose of toxoid the antitoxin titres of the twelve persons concerned were as follows: five showed 5 or more units per c.cm.; two showed 2.5 units; three at least 1 unit; one $>0.1 < 0.5$ unit; and one 0.01 unit per c.cm. of serum. Of the eleven sera available after an interval of a month the titre had fallen in two, four remained stationary, and the other five showed a further increase. However, of the twenty-six persons submitted to a *secondary* stimulus by 1 c.cm. of toxoid, two failed to develop tetanus antitoxin to a level of 0.1 unit per c.cm., although both of these did show a rapid increase in titre after the last injection.

Having thus shown the possibility of increasing the titre of tetanus antitoxin, it remains to observe to what extent

level, only one of whom failed to retain 0.1 unit (subject 16). The lowest residual level in this particular instance was approximately that shown about a year after the primary series, whereas the other eight persons for whom comparison was possible all showed a resting antitoxin titre definitely in excess of the previously determined levels.

In view of these further observations, we believe there is confirmatory evidence of the definite value of a primary series of tetanus toxoid injections when followed a year or two later by a *secondary* stimulus. Although the initial doses may be sufficient to ensure such a rapid antitoxin response as has been shown to occur, until a more accurate clinically protective standard is established than that conferred by the prophylactic dose of tetanus antitoxin it would seem desirable to maintain the titre of antitoxin in human serum at a minimum level of 0.1 unit per c.cm.

Summary

In a group of twelve persons the tetanus antitoxin level persisting two years after a primary series of three doses of tetanus toxoid has not fallen appreciably during the past year. A *secondary* stimulus of 1 c.cm. of toxoid given to these persons within a week effected a definite increase in titre, which persisted at significantly high levels after a month. Antitoxin titres similarly attained in a previous group are shown to persist after a year at or above the level of 0.1 unit per c.cm. of serum in nine of the total group of ten persons.

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TABLE II.—*Tetanus Antitoxin Response to the Injection of Tetanus Toxoid*

Subject Number	Following Primary Series		Following Fourth Dose		
	Maximum Response	After 12-15 Months	After 1 Week	After 1 Month	After 1 Year
	Units per c.cm. of serum				
2	0.5	$>0.1 < 0.5$	>5.0	5.0	0.75
5	$>0.001 < 0.1$	0.01	>0.1	$>0.1 < 1.0$	0.5
6	0.25	$>0.01 < 0.1$	>0.5	1.0	0.5
8	$>0.1 < 0.5$	$>0.01 < 0.1$	$>2.5 < 5.0$	$>2.5 < 5.0$	0.5
11	$>0.1 < 0.5$	$>0.01 < 0.1$	$>2.5 < 5.0$	2.5	0.25
12	$>0.1 < 0.5$	*	5.0	$>1.0 < 5.0$	0.25
14	0.1	$>0.001 < 0.1$	>1.0	1.0	0.25
16	$>0.01 < 0.1$	$>0.01 < 0.1$	0.5	$>0.5 < 1.0$	0.075
17	$>1.0 < 5.0$	$>0.1 < 0.25$	2.5	$>1.0 < 2.5$	0.5
19	$>0.1 < 0.25$	$>0.01 < 0.1$	$>2.5 < 5.0$	$>1.0 < 2.5$	$>0.1 < 0.5$

* Container broken.

these higher levels will persist. Ten persons (Table II) whose serum was obtained a year after the *secondary* stimulus showed a general fall in the residual antitoxin

Dr. A. Kissmeyer, writing in the Danish journal *Hospitalstidende* of May 31st, traces the response of venereal disease to treatment and public health measures in Denmark during the past fifty years. From 1885 to 1917 there was a steady rise in the notifications of both syphilis and gonorrhoea. A pronounced rise in 1918-19 has since been followed by a steady decline, which has resulted in the incidence of venereal disease at the present time being reduced to that of 1910. A comparison of Copenhagen with the rest of Denmark brought out the instructive fact that the former is making much more rapid progress than the latter. Between 1919 and 1933 the number of annual notifications of syphilis has fallen from 3,000 to 200. The corresponding fall in the rest of the country is from 1,400 to 400. The number of cases of congenital syphilis notified in Copenhagen between 1920 and 1933 has declined from 124 to 12, whereas in the rest of the country the decline has been only from 112 to 60. As for gonorrhoea, it is actually on the increase outside Copenhagen. The author notes that these figures upset the common belief that venereal disease is an urban rather than a country problem; and he suggests that the remarkable progress observed in Copenhagen should be traced to the efficiency of organization and treatment by whole-time specialists. In the country districts, on the other hand, gonorrhoea is increasing and syphilis is not declining as rapidly as it might because the provisions for their treatment are comparatively fortuitous.