COMPARISON OF RATE OF TITRE DROP AFTER ADEQUATE PENICILLIN THERAPY OF FIRST INFECTIONS AND RE-INFECTIONS IN SYPHILIS*

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In previous papers (Cutler and Harris, 1951; Cutler, Chester, and Price, 1953), dealing with the serologic response to treatment for syphilis, it has been shown that the rate of sero-reversal in adequately treated syphilis is, in general, related to the duration of infection before treatment. The generalization can be made that the longer the infection has been present before treatment, the longer will be the time required for sero-reversal.

In our experience with a large group of patients treated at the Venereal Disease Research Laboratory|| of the Public Health Service, it was our impression that the serologic response of the patient treated for a re-infection showed a slower rate of titre fall than in one treated for a first infection. With this in mind, the purpose of this study was to determine whether any such difference does exist in the rate of titre fall after adequate treatment for a first infection and for a re-infection.

Material

Initially, patients for the study were selected by the following criteria:

(1) If re-infected, both infections must have been treated by the Venereal Disease Research Laboratory.

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(2) Proof of a first and second infection must have been established by a positive dark field and/or serologic test.

(3) Treatment for the first infection must have been adequate, e.g., a minimum of 2.4 million units of penicillin. Any subsequent manifestations of infection following this type of treatment and in the light of contact history may then be assumed with a high degree of certainty to result from re-infection rather than relapse.¶

(4) The patient must have been free of lesions between the first and second infection.

(5) For re-infection to occur, the partner must have been found, through a later competent medical examination and contact interview, to have been, with a high degree of probability, in a communicable stage at the time coitus took place. This is judged by the time relationship between the appearance of lesions and the appearance of serologic evidence of infection of the partner.

A sizable group of patients was found to meet the above criteria. However, in the final selection, consideration had to be given to other factors known to affect the rate of fall of titre, and which should, then, be essentially similar in both the first infection and the re-infection before a valid comparison could be made:

- (1) Height of titre at time of treatment;
- (2) Duration of disease.

¶ The finding of a negative blood test between the first and second course of therapy was not considered necessary, for it is probable that cure takes place during the actual period of penicillinaemia, probably within the first 2 or 3 days, so that sero-positivity persists for a variable time after actual cure. Furthermore, our clinical experience has been that re-infections can occur regardless of height of titre (Magnuson, Thomas, Olansky, Kaplan, de Mello, and Cutler, 1956).

It would have been ideal if these factors could have been similar in first infection and in the re-infection of the same individual.

However, the time between treatment for the first infection and the exposure resulting in re-infection was often so short that a valid comparison could not be made of rate of titre fall between the two infections of a single individual.

Duration of disease and height of titre at time of treatment for the first infection and the re-infection also varied greatly in the same individual. Therefore, in order to have any factor constant, that of individual variation had to be disregarded.

It was therefore necessary to select four groups of patients. Two groups of patients considered to be re-infected and with readings of 64 and 128 Kahn units at the time of treatment for re-infection were selected for study. Similarly, two other groups of patients with adequate follow-up after treatment for a first infection and with titres of 64 and 128 Kahn units at treatment were also selected. Further selection of the latter group of patients was made so as to have the durations of individual infection as nearly as possible similar to those of the re-infected group.

It is fully realized that duration of disease cannot be known to the exact day, but with the rapport established with the patients and their contacts we feel certain that the error relative to the time element in the cases used is negligible. The classification of patients treated for the first infection and re-infection with respect to titre reading, range of time from probable infective exposure to treatment, and average time from exposure to treatment are given in Table I.

TABLE I

Kahn Units at Treatment	First Infection		Re-infection			
	Number of Patients	Time from Exposure to Treatment (days)		Number of Patients	Time from Exposure to Treatment (days)	
		Range	Average		Range	Average
64	12	40-136	69.8	10	44-118	70.2
128	10	62-118	92.6	10	62-110	97.8

As can be seen, the range and average time from exposure to treatment by titre are quite similar. A statistical test of variances of these factors between first infection and re-infection at 64 and 128 Kahn units revealed no significant differences. In all the patients used, the regularity of follow-up was considered to be satisfactory for a period of 21 weeks after treatment. After that time follow-up examinations were too infrequent, and several

cases were lost entirely to observation. However, since the object is to show the rate of serologic decrease rather than the number of patients becoming negative at various intervals, it is felt that, in the 21 weeks covered, there are sufficient data to permit comparison of the rates of decrease in serologic titre.

Method

For purposes of tabulation, Kahn units were converted to the highest serial dilution tube giving a positive reaction (Table II):

TABLE II

Tube	Dilution	Kahn Units
1	1:1	2, 3, 4
2	1:2	8
3	1:4	16
4	1:8	32
5	1:16	64
6	1:32	128
7	1:64	256

Kahn units of 0 and 1 were considered to be negative and were tabulated as no reaction (0 tubes).

For each of the four groups, weekly recordings of Kahn units were converted to serial dilution tubes and averaged. For plotting of these data the semi-logarithmic curve $\log y = a + bx$ was used, and provided an extremely good fit to the original data.

Results

In Fig. 1 (overleaf) data from the two groups of patients, one group treated for a first infection and the other for a re-infection and both having a titre of 64 Kahn units at the time of treatment, are compared. Similarly, Fig. 2 (overleaf) compares the other two groups with a titre of 128 Kahn units at the time of treatment. In both groups the titre drop was more rapid in those being treated for a first infection. A test of significance based upon the slopes of the trend lines for logarithms of the number of serial dilution tubes showed that, at both 64 and 128 Kahn units, the rate of fall among patients treated for a first infection was significantly faster than among those treated for a re-infection.

Discussion

It is felt that the method used for selecting the patients with a first infection to compare with those with a re-infection provides a group in which the factor of individual difference in response to treatment is minimized. Thus the factors compared are the rates of serologic fall from a given titre after treatment for first infection and re-infection.

It is evident that the rate of decrease in titre after treatment is slower after a re-infection than after a first infection.

Since previous studies have shown the relationship between rates of sero-reversal and stage of disease, it is felt that the findings here suggest that the differences may be related to changes in the immunologic mechanism of the body resulting from longer exposure of the body to *T. pallidum* in re-infection. Although it is known that the serologic titre cannot be considered as a measure of immunity, it is now known (Magnuson and others, 1956) that the serologic status as shown by the presence of reagin is related to the immune status, although the nature of the relationship is not yet clear. It is probable that the slower fall in serologic titre after a re-infection reflects an alteration in the response of the immune mechanism to *T. pallidum* which follows the increasing period of exposure to it, even though that period of exposure has been interrupted by a treatment-induced period of freedom from infection.

Summary

The rate of decrease of Kahn titre in a group of patients treated for a first infection with *T. pallidum* and in another group treated for re-infection is compared with respect to duration of infection and height of serologic titre at time of treatment. After adequate therapy, the rate of fall of the serologic titre from a given level is significantly more rapid after treatment for a first infection than after treatment for a re-infection.

It is suggested that this difference is a reflection of immunologic changes resulting from a larger immunologic stimulus in re-infection.

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