THE TREATMENT OF EARLY SYPHILIS WITH CRYSTALLINE PENICILLIN G IN PEANUT OIL AND BEESWAX (P. O. B.) EMPLOYING A TREATMENT SCHEDULE OF 300,000 UNITS GIVEN TWICE A WEEK FOR A PERIOD OF 8 WEEKS*

Report of 113 Cases

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In the evaluation of syphilis therapy with penicillin, it has become increasingly evident that the optimum treatment schedule has not yet been determined. The questions of solution versus delayed absorption or excretion preparations, continuous or discontinuous treatment, time interval, etc., are still the subjects of extensive laboratory and clinical investigation.

In a recent study (1) we reported on a continuous schedule of syphilis therapy in which penicillin was administered once a day for sixteen consecutive days. In this plan, it is assumed that there is a continuous effective concentration of penicillin in the blood and tissues during the entire treatment course. This schedule gave excellent clinical and serologic results and compared favorably with the best schedules of syphilis therapy; however, the results were by no means optimal.

The suggestion has variously been made that perhaps a broken schedule of therapy in which penicillin is administered at relatively long intervals may produce equally good results and perhaps it is not necessary to have a continuous concentration of penicillin in the blood and tissues to obtain optimal results. It was with this in mind that the present study was undertaken.

In this investigation we are reporting on such an extended discontinuous treatment schedule in which penicillin-oil-beeswax (P.O.B.) semifluid type was given twice a week at intervals of three to four days. In this form of therapy it may be safely assumed that there are relatively long periods of freedom from detectable penicillin concentration in the blood.

One hundred sixty patients were subjected to this form of therapy. The treatments were given in ambulatory clinic practice, and so mapped as not to interfere in any way with the patients' normal routine. The treatments were administered in the clinic at semi-weekly intervals, for an eight-weeks period. Each dose was 300,000 units of P.O.B.; the total dose was therefore 4,800,000 units. This is exactly that employed in our previous sixteen-day continuous treatment schedule.

Of the total treated, 113 cases or seventy per cent, remained under observation

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for a period of eight months or longer following termination of treatment and these constitute the basis of this report. A minimum of eight months post-treatment observation was required in the cases, firstly, because relapses are usually observed before the end of the eighth month and secondly, this eight-months follow-up period was employed in evaluating the continuous treatment schedule mentioned above. Thus it was possible for us to compare the two schedules on an equal observation time basis.

The patients were of both sexes; 78 were males and 35 females; 84 were non-white and 29 white patients. The ages varied from 19 to 55 years (Table I).

The blood specimens of all the patients were subjected to a battery of serologic tests identical with those employed in our previous study; this too was for the purpose of being able to compare the results in the two studies. The tests were

TABLE I

Color and sex distribution of 113 patients treated

		WHITE	NON-WHITE
Male	78	25	53
Female	35	4	31
Total	113	29	84

TABLE II

Classification of the 113 patients according to diagnosis

ORIGINAL DIAGNOSIS	UNDER OBSERVATION	
	Patients	Per cent
Seronegative primary	8	7.1
Seropositive primary	40	35.4
Secondary	65	57.5
Total	113	

the Mazzini, V.D.R.L. (Venereal Disease Research Laboratory) Cardiolipin, Kline Exclusion, Rein-Bossak Cardiolipin (microflocculation test), Kolmer Complement fixation test and a Cardiolipin Complement fixation test. Blood tests were performed at monthly intervals with the exception that in the seronegative primary cases they were done at bi-weekly intervals. All tests were processed in a single laboratory by the same technicians at the New York Skin and Cancer Unit, in order to avoid technical differences.

The cases treated were divided into the standard classification of seronegative primary, seropositive primary and secondary syphilis. The diagnosis of seronegative primary syphilis was based on clinical grounds as well as on a positive darkfield examination. In addition to the clinical and often bacteriologic evidence, a positive serologic test was present in the seropositive primary cases.

Secondary syphilis was diagnosed on clinical evidence and the presence of a positive serologic test; in many cases darkfield examinations proved positive. The division of the cases according to the mentioned classification appears in Table II.

The clinical response to therapy in all instances was uniformly satisfactory and differed in no wise from the usual experience in short term schedules. Although, as stated, a battery of tests was performed in all cases, the Mazzini test alone was employed as the criterion for evaluating the material. This test was likewise employed in evaluating the sixteen-day schedule previously reported.

RESULTS

The analysis of the results of therapy in the various groups is as follows:

1. *Seronegative primary.* Eight of the 12 cases were followed from eight to seventeen months. All but one remained seronegative. The failure was a clinical relapse twelve months post treatment. While this case is listed as a treatment failure, he may well have been a reinfection. For a period of five months post treatment, five serologic tests taken at monthly intervals proved negative. The patient absented himself for seven months and returned presenting a generalized maculo-papular eruption of the type seen in the very early lues (clinically it resembled in no wise a relapsing syphilid). A history of repeated exposures was obtained.

Of the four cases that were lost from observation before the eighth month, one was negative at four months and three at five months, post treatment.

2. *Seropositive primary cases.* Of a total of 40 cases followed from eight to seventeen months post-termination of treatment, 37 (92.5%) became seronegative, 2 (5.0%) showed satisfactory serologic progress (1–2 units) and 1 (2.5%) was a clinical failure.

3. *Secondary cases.* Of 65 followed from eight to nineteen months, 41 (63.1%) became seronegative, 14 (21.5%) showed a satisfactory serologic response (1–4 units), 4 (6.9%) showed unsatisfactory serologic progress (8 or more units), and 6 (9.2%) were clinical failures.

The drop in the serologic titre in the treated patients that have not attained seronegativity but still remain under observation is detailed in Table III.

It will be observed that practically all cases showed a marked drop in the serologic titre, indicating definite tendency toward seronegativity, but only those are regarded as satisfactory in which the test had dropped to less than four units. Findings above this figure we regard as unsatisfactory, and are classified as serologic failures. Based upon this classification 16 (80%) of the cases showed a satisfactory trend and 4 (20%) one that is not satisfactory. Of the unsatisfactory cases one showed a titre of eight at the end of seventeen months; another a titre of eight at sixteen months; the third, sixteen units at the end of fourteen months (although the drop in this case was from an initial of 512 units) and the fourth at the end of eight months, a titre of eight units. It is not unlikely that most of these will completely fade out in the course of time without any further therapy; this is common experience. On the other hand it is possible that some

of the satisfactory cases with very low titres may relapse and become unsatisfactory (Table III).

In connection with low titre serologic reactions in treated syphilis it is well to point out that there is considerable evidence indicating that low titre serologic reactions may in some instances really represent biologic false positive reactions, for it has been observed that intercurrent infections, which usually raises the serologic titre in false positive cases will do the same in low titre syphilis cases (2).

TABLE III

Serologic drop in titre in cases still under observation
total—20 cases

DIAGNOSIS	TITRE AT ONSET	TITRE AT PRESENT	DURATION OF OBSERVATION
	Seropositive primary		
			months
1. J. J.	4	1	9
2. H. G.	64	2	14
	Secondary		
3. M. B.	32	2	16
4. F. B.	32	1	15
5. R. B.	128	8	16
6. T. B.	64	2	10
7. C. C.	64	8	17
8. M. F.	32	2	11
9. L. V.	256	2	13
10. A. M.	64	2	9
11. C. Mc.	64	1	12
12. E. P.	8	4	11
13. R. G.	64	8	8
14. H. R.	512	16	14
15. R. T.	32	4	8
16. N. W.	256	2	18
17. A. R.	32	4	10
18. L. G.	4	2	11
19. E. J.	128	4	18
20. M. W.	64	2	14

Clinical failures: There were eight clinical failures (relapses or reinfections). The appended table (Table IV) furnishes the pertinent data in each case. While some of the cases are undoubted relapses, in two (Cases 1 and 6) there is a strong supposition that they are reinfections. It is difficult to prove the point one way or the other.

Reactions: Remarkably few treatment reactions were observed and these consisted of itching and several cases showing mild urticarial eruptions. This parallels our findings in our sixteen-day schedule series when the semifluid P.O.B. was used in therapy.

Spinal fluid examination: Fifty-one patients were subjected to lumbar puncture eight months or longer post treatment. All but three gave normal findings. The abnormal findings the the three are: Case 1 (R. G.) original diagnosis secondary syphilis; showed a serorelapse, 92 cells, Kolmer 4+, T.P. 38 mg.%, Col. Gold 2211000000. Case 2 (R. B.) original diagnosis secondary syphilis, showed a Kolmer 4+, T.P. 38 mg.%, Col. Gold 3222100000. Case 3 (M. F.) a case of secondary

TABLE IV

Analysis of patients showing relapses or reinfections
total—8 patients

PATIENT	STAGE OF DISEASE	MONTHS POST TREATMENT OF RELAPSE OR REINFECTION	NATURE OF RELAPSE
1. D. B.....	Seronegative Primary	12	Generalized secondaries
2. J. W.....	Seropositive Primary	11	Mucocutaneous relapse
3. Y. Y.....	Secondary	4	Generalized secondaries
4. D. T.....	Secondary	4	Generalized secondaries
5. H. S.....	Secondary	12	Mucocutaneous relapse
6. M. M.....	Secondary	10	Penile primary
7. W. B.....	Secondary	10	Generalized secondaries
8. A. L.....	Secondary	8	Single papule on scrotum

TABLE V

Summary and comparison of results of therapy with P.O.B.

	CHARGIN ET AL. 300,000 UNITS DAILY TOTAL DOSAGE 4,800,000		SOBEL ET AL. 300,000 UNITS TWICE WEEKLY TOTAL DOSAGE 4,800,000	
	No.	Per cent	No.	Per cent
Seronegative primary.....	13	100.0	8	100.0
Remained seronegative.....	13	100.0	7	87.5
Relapse or reinfection.....	0	0.0	1	12.5
Seropositive primary.....	51	100.0	40	100.0
Became negative.....	47	92.2	37	92.5
Remained positive.....	2	4.0	2	5.0
Relapse or reinfection.....	2	4.0	1	2.5
Secondary.....	83	100.0	65	100.0
Became negative.....	62	74.7	41	63.1
Remained positive.....	17	20.5	18	27.7
Relapse or reinfection.....	4	4.8	6	9.2

syphilis, showed a cell count of 13, Kolmer negative, T.P. 19 mg.%, Col. Gold negative.

The abnormal spinal fluid findings represent 6% of those performed, which is much higher than in our sixteen-day series in which only one abnormal fluid was found (increased cell count) in 90 cases.

Comparing this series with the sixteen-day series, Table V, shows that in seronegative primary syphilis the results are comparable. The single failure re-

ported in the twice-weekly series may have been a reinfection. In the seropositive primary cases the results are almost identical; although there is a slight difference in favor of the two-a-week therapy. The difference is not statistically significant. In the secondary syphilis cases all three subdivisions show a poorer result by the two-a-week as compared to the sixteen-day schedule. Sixty-three per cent of the former against seventy-four per cent became seronegative. Twenty-seven per cent of the former against twenty per cent of the latter remained seropositive; and 9.2% against 4.8% had clinical relapses or reinfections.

COMMENT

The semi-weekly schedule of therapy lends itself very well to ambulatory treatment since it interferes little with the normal routine of patients. However, lapses from regular treatment so commonly observed in pre-penicillin days also occur with this plan of treatment and must be counted against the semi-weekly schedule. In this study twenty per cent of the patients originally placed under treatment failed to take the full course of therapy. Many of these cases necessarily remain reservoirs of infection because of inadequate therapy.

It is now possible to state that in primary syphilis, seronegative or seropositive, all schedules of therapy give eminently satisfactory results. While they differ, it is only to a slight degree. However, in secondary syphilis this does not hold true.

While some schedules give better results than others, none rates very high. It is in this stage of syphilis that improved therapy is required and perhaps this can be accomplished by additive treatment. It is with this in mind that we have inaugurated a combined schedule of penicillin, arsenic and bismuth which should furnish information respecting this important phase of syphilis therapy.

CONCLUSIONS

1. The twice-a-week schedule lends itself very well to ambulatory treatment.
2. Twenty per cent of the patients admitted did not complete treatment; they constitute a source of new infections.
3. Seventy per cent of the patients who completed treatment remained under observation for eight to nineteen months, post-treatment.
4. The results in primary syphilis, seronegative and seropositive, compare favorably with the sixteen-day schedule of treatment.
5. In secondary syphilis the results are less satisfactory.
6. The spinal fluid results show a higher percentage of abnormal findings with the twice-a-week schedule than with the 16-day schedule.

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