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BENZATHINE PENICILLIN G IN THE TREATMENT OF SYPHILIS *

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SYNOPSIS

Post-treatment observation of two years' duration has confirmed preliminary data which indicated that a single injection of 2.5 million units of benzathine penicillin G, in early infectious syphilis, produces results equal, if not superior, to those obtained with schedules employing 4.8 million units of procaine penicillin and aluminium monostearate.

Preliminary data suggest that a single injection of 2.4 or 2.5 million units of benzathine penicillin G may be inadequate for the treatment of asymptomatic neurosyphilis.

Delayed reactions do not appear to be induced by the long-sustained blood-levels following the administration of benzathine penicillin G.

Repeated injections of PAM increase the risk of reaction to treatment.

The report of the effectiveness of penicillin in the treatment of syphilis in 1943 represented a highly significant milestone in our attempts to control syphilis, and the following years have witnessed the determination of the optimum methods of use of penicillin in the various stages of syphilis and the development of numerous dosage-forms and compounds of penicillin, each with advantages over those preceding.

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The introduction of each new penicillin preparation has necessitated painstaking clinical investigation in order to determine its effectiveness in the treatment of syphilis, and consequently its possible role in public health control programmes. The development of the delayed-absorption types of penicillin preparations has simplified the treatment of the individual patient and has made possible the mass treatment programmes against the treponematoses which have been found so highly successful throughout the world.

The experience with procaine penicillin G in oil with 2% aluminium monostearate (PAM) is by now well documented, both from carefully controlled clinical studies, such as those conducted by the United States Public Health Service Venereal Disease Program, and from mass treatment programmes—e.g., those carried out by the United States Public Health Service against syphilis in the Virgin Islands and among the Navajo Indians, and those undertaken by the World Health Organization against syphilis and yaws in many parts of the world. Within the last few years we have seen the development of benzathine penicillin G, a preparation which in a dosage of 2.4 million units maintains in most patients a detectable blood-level for periods up to four weeks. In our own experience we have found this preparation highly effective in the treatment of primary and secondary syphilis.

In this report our experience with benzathine penicillin G in the treatment of early syphilis is described, and formally, for the first time, our experience with benzathine penicillin G in the treatment of asymptomatic neurosyphilis is reported.

Early Syphilis

Preliminary reports [3, 4] of the efficacy of this preparation indicated that the results achieved in early syphilis with 2.5 million units were equivalent, if not superior, to those obtained with schedules employing 4.8 million units of procaine penicillin and aluminium monostearate. The excellent results noted in these earlier reports have now been confirmed by a larger group of cases with an observation period of more than two years. A comparison of benzathine penicillin G and PAM is presented in Table I.

In addition to showing results in the secondary stage as a basis for comparison between schedules, this table also shows results following the treatment of primary syphilis with benzathine penicillin G. To date there have been no failures among 52 patients treated for seronegative primary syphilis, 27 of whom have been observed for more than a year and 11 for more than two years. Among 67 patients with seropositive primary syphilis, two patients, or a cumulative rate of 4.0%, have required further treatment, one for serological relapse and one for reinfection. The largest group comprises 155 patients treated for secondary syphilis, 90 of whom were observed for more than one year and 37 for more than two years. The cumulative

TABLE I. COMPARISON OF BENZATHINE PENICILLIN G AND PAM IN THE TREATMENT OF SECONDARY SYPHILIS

Schedule of treatment	Stage of syphilis	Number of cases			Results 2 years after treatment			
					cumulative percentage re-treated			percentage sero-negative *
		total	observed for more than:		total	clinical or sero-logical failure	re-infection	
			1 year	2 years				
Benzathine penicillin G (2.5 million units, 1 injection)	Seronegative primary	52	27	11	0.0	—	—	100.0
	Seropositive primary	67	33	13	4.0	2.0	2.0	96.0
	Secondary	155	90	37	5.5	0.9	4.6	94.5
PAM (4.8 million units)								
single session	Secondary	166	117	83	7.7	3.8	3.9	91.0
2-4 sessions	Secondary	415	241	91	11.7	7.8	3.9	88.3

* Negative or less than 4 Kahn units

re-treatment rate is 5.5% (0.9% serological or clinical failure and 4.6% reinfection). The seronegativity rates for the three stages two years after treatment are 100.0% for seronegative primary, 96.0% for seropositive primary, and 94.5% for secondary syphilis.

It will be noted that the results following treatment of secondary syphilis with benzathine penicillin G are slightly better than those obtained with 4.8 million units of PAM, administered either in a single session or in two, three or four sessions. The seronegativity rates two years following treatment are 91.0% for the single-session schedule and 88.3% for the divided-dosage schedules. Cumulative re-treatment rates are 7.7% and 11.7%, respectively. If reinfections are considered as successful treatment results, all three schedules shown are better than 92% effective for the treatment of secondary syphilis.

Asymptomatic Neurosyphilis

Schedules of treatment which are effective for secondary syphilis are generally considered adequate for the treatment of latent syphilis. However, in areas where lack of clinical facilities preclude complete spinal fluid evaluation, it is not always possible to rule out the presence of asymptomatic neurosyphilis in patients who have been diagnosed as latent. If it could be established that schedules employed for latent syphilis were also adequate for asymptomatic neurosyphilis, then the necessity for routine spinal fluid examinations among apparently latent syphilitics would be obviated.

Since the benzathine penicillin G is now used almost exclusively in some States of the USA for the treatment of syphilis, it seems advisable at this time to determine if this preparation, which has proved so effective in the treatment of early syphilis, is, in the same scheduled dosage, adequate for the successful treatment of asymptomatic neurosyphilis. The same treatment centres that co-operated in the early syphilis evaluation were requested to treat patients with a diagnosis of asymptomatic neurosyphilis with the early syphilis schedule of 2.5 million units of benzathine penicillin G administered in a single injection. In order to ensure the comparability of tests of patients treated at the various participating clinics, blood and spinal fluid specimens are sent to the Venereal Disease Research Laboratory at Chamblee, Ga., where the Kolmer quantitative, VDRL and total protein determination tests are performed. The cell count is done by the treatment clinic and, since treatment is instituted before the complete spinal fluid analysis, only patients with 20 or more cells before treatment are included in the evaluation.

The study to date includes 47 patients with asymptomatic neurosyphilis who have been observed for periods of from three months to two years following treatment with 2.5 (or, in 16 cases, 2.4) million units of benzathine penicillin G. A series of 53 patients with asymptomatic neurosyphilis treated with other penicillin G preparations (aqueous, POB, or PAM) in amounts ranging from 4.0 to 5.9 million units is used for comparison in the following discussion.

The two groups are similar in that patients in both groups had positive complement-fixation tests in the spinal fluid and a minimum pre-treatment cell count of 20. As shown in Fig. 1, the distribution of cases by pre-treatment cell count is approximately the same, the differences in the two ranging from 0.2% for patients with 150 cells or more to 4.7% for patients with 100-149 cells.

The pre-treatment total protein content was slightly lower in patients treated with benzathine penicillin G than in patients treated with other penicillin G preparations, the median being 46 mg per 100 ml as against 55 mg per 100 ml. Since the tests were performed at different laboratories, this might well reflect a difference in technique.

Although the degree of positivity of the spinal fluid in the two groups is approximately the same, the benzathine penicillin G series includes more older patients (and therefore patients with syphilis of longer duration), more untreated syphilis, more males, and more Negroes than the series treated with other penicillin G preparations. To what extent these factors influenced the results of treatment is impossible to determine from the small series presented here. In general, the race distribution would tend to favour better treatment results from benzathine penicillin G since Negroes respond more readily to treatment;[a] the younger ages and shorter duration of

[a] Based upon results obtained in co-operative clinical studies carried out by the United States Public Health Service.[2]

FIG. 1. PERCENTAGE DISTRIBUTION OF CASES OF ASYMPTOMATIC NEUROSYPHILIS BY PRE-TREATMENT CELL COUNT

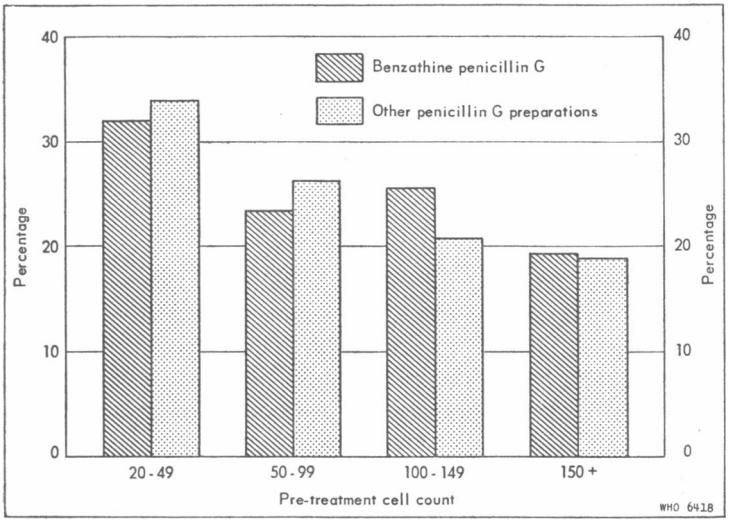
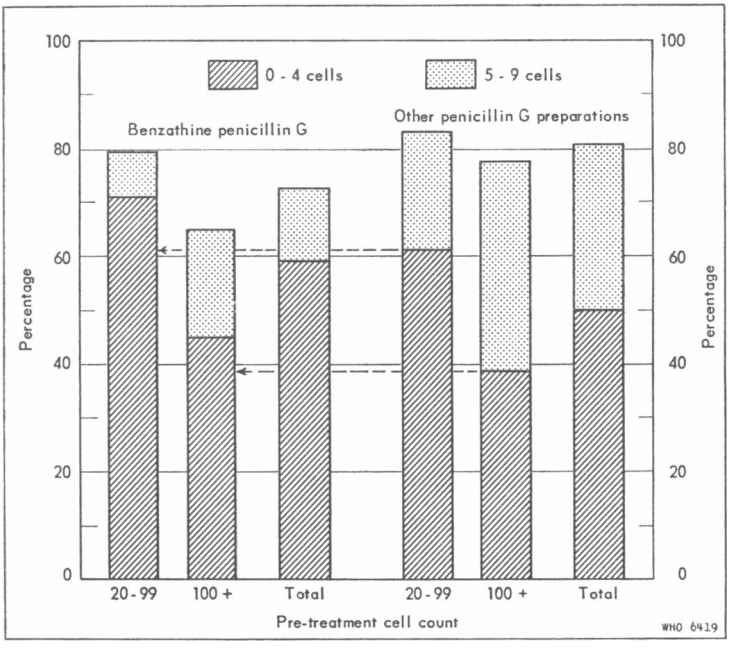


FIG. 2. PERCENTAGE OF PATIENTS WITH NORMAL CELL COUNT 3 MONTHS AFTER TREATMENT FOR ASYMPTOMATIC NEUROSYPHILIS



infection would influence treatment results in favour of the other penicillin G preparations.

Since the number of cells in the spinal fluid is one of the first indications of response to treatment to appear, the cell count is used in Fig. 2 as a measure of comparison of results at the third month following treatment. The solid portion of the bars represents patients with a normal cell count (0-4); the shaded portion represents patients with a near-normal cell count (5-9). Of the patients with a pre-treatment cell count of 20-99, 71% had a completely normal cell count three months after treatment with benzathine penicillin G. The rate was lower (45%) among patients with a pre-treatment cell count of 100 or more.

Among patients treated with other penicillin G preparations, the percentage with a completely normal cell count was slightly lower both in patients with 20-99 cells and in those with 100 or more cells than among patients treated with benzathine penicillin G (indicated by arrows). However, when patients with a near-normal cell count are included, this slight difference between treatments is reversed.

Fig. 3 is a companion chart showing results one year following treatment. The differences observed at the third month between patients with pre-treatment cell counts of 20-99 and of 100 or more and between types of penicillin have practically disappeared.

The residual percentages of patients who did not attain normal and near-normal cell counts within a year after treatment represent cases which are potential treatment failures. This side of the picture is presented in Fig. 4, which compares the cumulative spinal fluid relapse rate in the two series. By the eighteenth month following treatment, 21% of the patients treated with benzathine penicillin G had relapsed as compared with 10.5% of patients treated with other penicillin G preparations. Twenty-five months after treatment the relapse rate in this latter group had climbed to 15.8%. If a similar increase occurs among patients treated with benzathine penicillin G, it will place the relapse rate well above 25% after two years of follow-up. On the other hand, if no more cases relapse as the percentage of patients observed increases, the relapse rate of 21% at eighteen months will be reduced. These preliminary data suggest, however, that it may be necessary to increase the dosage of 2.5 million units of benzathine penicillin G for the treatment of asymptomatic neurosyphilis—and for apparent latent syphilis if spinal fluid evaluation is not possible.

Reactions to Treatment

In addition to the effectiveness of a penicillin preparation, its toxicity is of considerable importance in the conduct of venereal disease control programmes, for the impression has been created that the use of penicillin is fraught with significant danger of reaction. This has led some to question

FIG. 3. PERCENTAGE OF PATIENTS WITH NORMAL CELL COUNT ONE YEAR AFTER TREATMENT FOR ASYMPTOMATIC NEUROSYPHILIS

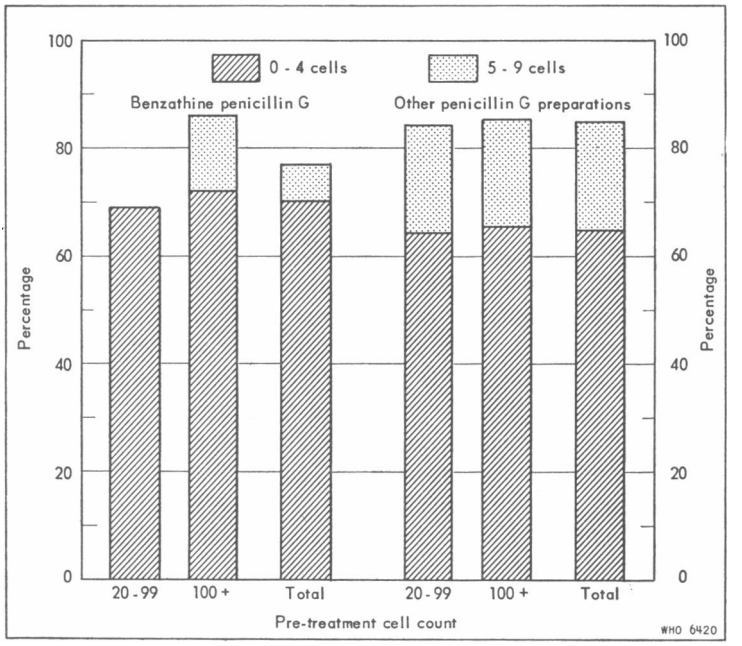
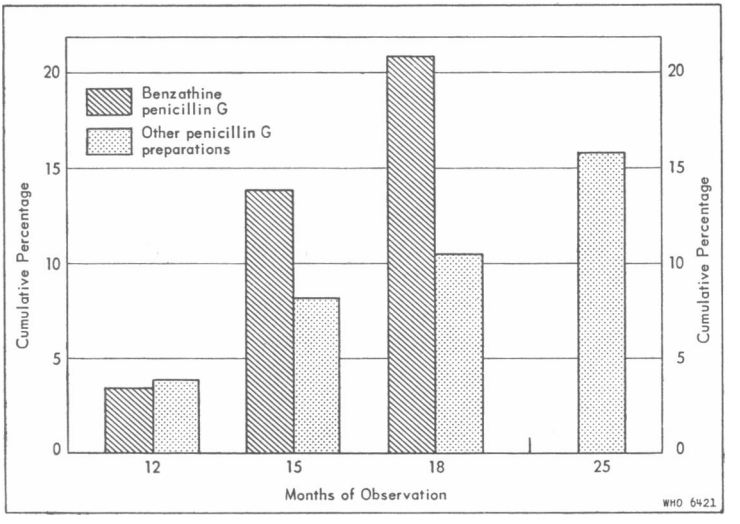


FIG. 4. CUMULATIVE SPINAL FLUID RELAPSE RATE AMONG PATIENTS TREATED FOR ASYMPTOMATIC NEUROSYPHILIS



the desirability of using penicillin in mass treatment programmes of the type which is necessary for control operations in certain circumstances. Our experience has shown that this fear is groundless, and the report of our findings which follows may be of significant interest.

In a previous report [4] on 16 345 patients treated with penicillin at 24 prevention and control centres, it was observed that reactions to penicillin apparently occurred less frequently among clinic patients than among patients treated in private practice. This was attributed to the large proportion of Negroes and young adults in venereal disease clinic populations—two groups which tolerate penicillin well.

Reactions to penicillin were reported in 109 of the 16 345 patients treated. Urticaria, the most frequent reaction, was observed in 90 patients. Four anaphylactoid reactions occurred—all following the administration of PAM. Unfortunately, the study included approximately 12 000 patients treated with PAM and only 4000 patients treated with benzathine penicillin G. Since anaphylactic shock occurred in approximately 1 in every 4000 treated, no significance could be attached to the fact that none was observed among patients treated with benzathine penicillin G. And, too, although not observed during the period covered by the reaction study, anaphylactic shock has been known to occur following the administration of benzathine penicillin G.[1]

The rate per 1000 patients treated was 7.96 for PAM as against 2.54 for benzathine penicillin G. The difference, it was reasoned, could have been due to longer treatment schedules and therefore a greater opportunity for observance of reactions to PAM than to benzathine penicillin G, which is usually administered in one injection. This reasoning seemed justified, since no significant difference was noted between the two types of penicillin when both were administered in a single session.

Since our earlier report, almost 3200 patients treated with benzathine penicillin G have been added to the series, making a total of 7109 patients treated with this type of penicillin. The incidence of reactions has remained about the same—2.39 per 1000 patients treated.

The additional cases were contributed by only one treatment clinic—the Chicago Municipal Social Hygiene Clinic. For this reason the following comparisons between benzathine penicillin G and PAM will be limited to cases treated at this one clinic. The reaction rates following both penicillin preparations were low—2.20 per 1000 patients treated with benzathine penicillin G and 4.52 per 1000 treated with PAM. In both groups more than two-thirds of the patients were under 30 years of age and more than 90% were Negroes. Urticaria was the principal reaction reported, accounting for 6 of the 7 reactions to benzathine penicillin G and for 12 of the 15 reactions to PAM. One patient treated with benzathine penicillin G complained of nausea and vomiting. The other three reactions to PAM were dyspnoea, generalized pruritus, and anaphylactic shock.

Benzathine penicillin G was administered in one injection. Although PAM was given in one injection for gonorrhoea and as epidemiological treatment, schedules for syphilis varied from a few days to as long as three weeks. A comparison of the incidence of reactions to the two penicillin preparations by type of case treated is shown in Table II. The greatest difference was observed among patients treated for syphilis—19 for benzathine penicillin G as against 74 for PAM. As discussed previously, the longer duration of the PAM schedules afforded an opportunity for reactions to be observed.

TABLE II. COMPARISON OF REACTION RATES PER 1000 PATIENTS TREATED WITH BENZATHINE PENICILLIN G AND PROCAINE PENICILLIN AND ALUMINIUM MONOSTEARATE

Type of case treated	Benzathine penicillin G			Procaine penicillin and aluminium monostearate		
	total cases	cases reacting		total cases	cases reacting	
		number	rate		number	rate
Epidemiological treatment	854	3	4	1032	2	2
Gonorrhoea	2206	2	1	2147	3	1
Syphilis	108	2	19	136	10	74
Other	20	—	0	1	—	0
Total	3188	7	2.2	3316	15	4.5

A review of these cases, however, revealed that in all but three instances, reactions occurred either immediately after the initial injection of penicillin or after the scheduled course of treatment had been completed; that is, the relationship between reporting of reactions and completion of treatment suggests that there was no factor which would have caused the PAM and not the benzathine penicillin G cases to return to report reaction. In other words, only three of the 15 reactions to PAM might have been unreported had these three patients not returned for further treatment.

In the benzathine penicillin G series, no reactions were observed beyond the fourth day following treatment; in the PAM series, two-thirds of the reactions occurred *after* the fourth day following the initial injection. This would suggest (1) that benzathine penicillin G, which maintains a detectable blood-level for several weeks, does not tend to produce delayed reactions; and (2) that repeated injections of PAM increase the risk of reactions to treatment.

RÉSUMÉ

L'injection unique de 2,5 millions d'unités de benzathine pénicilline G est efficace dans le traitement de la syphilis récente. Les résultats observés après le traitement sont équivalents à ceux qu'ont donnés des schémas comportant l'injection de 4 800 000 unités de pénicilline procaïnée additionnée de monostéarate d'aluminium. Des malades atteints de syphilis nerveuse asymptomatique ont reçu 2,4 ou 2,5 millions d'unités de benzathine pénicilline G et les résultats ont été comparés à ceux qu'on a obtenus sur un groupe analogue de malades traités par d'autres préparations de pénicilline G. Il semble ressortir de cette étude qu'il pourrait être nécessaire d'accroître la dose administrée pour traiter la syphilis nerveuse asymptomatique et la syphilis latente. L'incidence des réactions chez les malades traités par la benzathine pénicilline G était de 2,39 pour 1000. Des études sur les réactions à la pénicilline montrent que la benzathine pénicilline G, qui entretient une pénicillinémie décelable pendant plusieurs semaines, ne tend pas à susciter de réactions différées, alors que les injections réitérées de PAM paraissent accroître le risque de réactions au traitement.

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