A Reappraisal of Benzathine Penicillin in Gonorrhea Control

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THOSE concerned with public health problems have been frustrated in attempts at reduction of the high incidence of gonorrhea. Penicillin therapy, combined with carefully perfected epidemiological procedures, resulted in a tremendous decrease in morbidity from primary and secondary syphilis. The utilization of the same drug, in conjunction with epidemiology modified to fit the needs of gonorrhea, has resulted in only a modest decrease in reported cases of gonorrhea over the last 10 to 12 years.

Recent attempts at solution of the problem of gonorrhea control have been based upon the modifications of epidemiological procedures and therapy. Efforts directed toward modifying the epidemiological procedures resulted in the adoption of what was known as "speed zone" epidemiology. When this approach failed to produce overall outstanding results, long-acting penicillin was added to the former therapeutic regimens to try to produce a period of "antibiotic quarantine" during which the patient could not be reinfected. The objective of this form of therapy was to decrease the incidence of gonorrhea.

Male patients of the venereal disease clinic of the Houston Health Department were treated with benzathine penicillin in addition to the usual procaine penicillin regimen, following in general a method reported by Hookings and Graves (*1*), for two purposes. The first was to find whether, by this means, male patients with gonorrhea could be adequately treated and effectively protected by an antibiotic quarantine against reinfection for 32 days. The second purpose was to determine the efficacy of the method in reducing the incidence of gonorrhea.

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Methods and Results

All male patients coming to our clinic for the first time with a clinical diagnosis of gonorrhea, except those sensitive to penicillin, were treated on one of four regimens, and are included in this study. Calendar periods during which the regimens were used were as follows:

Time interval	*Treatment schedule*	*Number patients*
Apr. 1, 1954, to Mar. 31, 1955.	600,000 units procaine penicillin with 2 percent aluminum monostearate in oil (PAM).	958
Apr. 1, 1956, to Mar. 31, 1957.	600,000 units benzathine penicillin.	1,075
Apr. 1, 1957, to June 1, 1958.	900,000 units PAM and 900,000 units benzathine penicillin.	1,331
Nov. 10, 1958, to Feb. 20, 1959.	1,200,000 units aqueous procaine penicillin and 1,200,000 units benzathine penicillin.	258

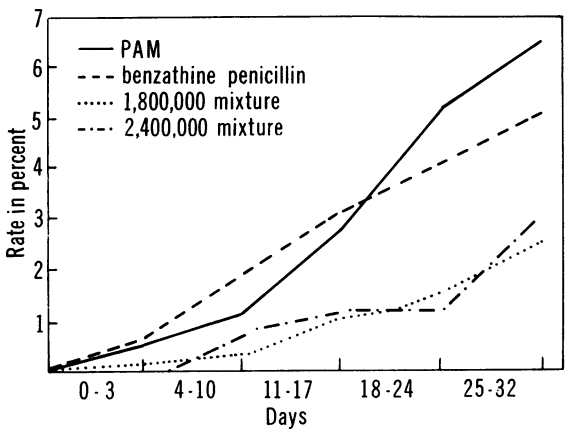
The patients were carried through our regular clinic routine. Contact investigation was carried out, and sex contacts were treated. No attempt was made to determine whether study patients had relapsed or were reinfected. Any

study patient who was again diagnosed and treated for clinical gonorrhea during the observation periods is considered a treatment failure.

During most of the period covered by this study, bacterial cultures were not available to us as a routine diagnostic aid. For this reason all patients were diagnosed on clinical findings and subsequently treated. When bacterial cultures became available late in this study period, we made a comparison between two groups of patients. One group consisting of 258 patients were diagnosed on clinical grounds; the other group of 448 patients were diagnosed on cultural grounds. We found no significant differences in retreatment rates between these two groups. Patients with nongonococcal urethritis composed only a minute fraction of men coming to our clinic for the first time with acute anterior urethritis.

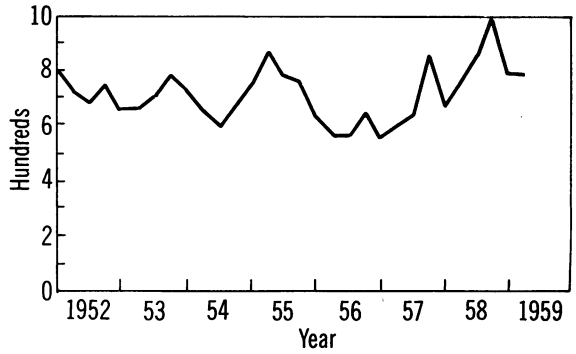
Retreatment rates for the first 32 days following therapy in the four schedules are shown in figure 1.

Figure 1. Cumulative retreatment rates for 3,622 male gonorrhea patients in 32 days following therapy, Houston, 1954–59



In brief, these data show the higher cumulative retreatment rates at the end of the 25- to 32-day period were with the single agents when used in smaller dosages. The lower retreatment rates were achieved by combining the short-acting and long-acting agents, with concomitant increase in the total dose given. These lower retreatment rates may be due to fewer relapses, fewer reinfections, or other intangible

Figure 2. Gonorrhea morbidity, Houston Venereal Disease Clinic, 1952–59



factors. These rates suggest that patients were indeed protected from reinfection by the period of antibiotic quarantine secondary to prolonged penicillin blood levels.

If this reduction in return rates is to be of more than academic interest, it must somehow affect gonorrhea incidence. In Houston we were unable to show any effect on incidence, because the actual incidence of gonorrhea is unknown, due to minimal case reporting by private physicians. We do have, however, exact figures for our clinic gonorrhea morbidity (fig. 2). We find no correlation between these morbidity figures and the application of our various treatment schedules.

Since we needed a means of evaluating the efficacy of these schedules, we extended our period of observation from 4 weeks (25–32 days) to 16 weeks. By so doing, we obtained an internal comparison of relapse/reinfection rates among the several schedules. With this extended observation period, the cumulative retreatment rates vary only from 13.89 percent to 17.42 percent between the several therapeutic regimens (fig 3). The maximal difference lies between two very similar schedules, both utilizing mixtures containing the long-acting drug.

When a study such as this is conducted over a long period of time, there is always chance that factors other than the controlled ones will influence results. During the period when the 2,400,000 unit mixture was administered, 19.3 percent more cases of gonorrhea were seen in the Houston clinic than in the time period when the treatment schedule was 600,000 units of PAM. It seems reasonable to believe that if the chance of acquiring gonorrhea in this popu-

lation was one-fifth greater during the time of treatment with a 2.4 million unit schedule than during the period of treatment with 600,000 units of PAM, then the chance of reinfection of those treated would also be one-fifth greater.

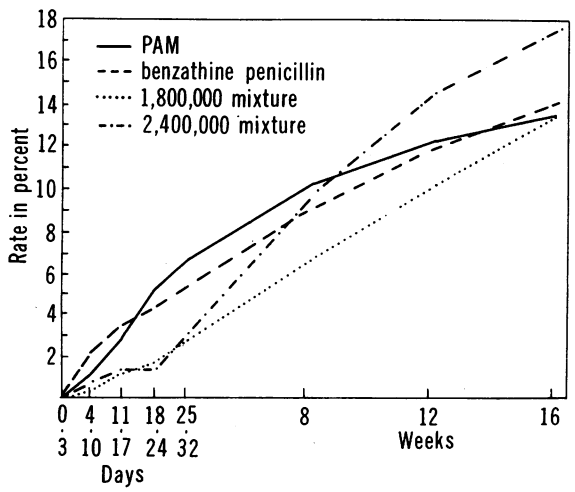
Adjusting the 16-week retreatment rate for this increase in probability of becoming reinfected, a retreatment rate of 14.06 is derived for the 2.4 million unit schedule, as compared with 14.00 for the 600,000 unit schedule. When this adjustment is made, the foregoing studies all show quite similar retreatment rates at the end point.

It is interesting to note that investigators in Great Britain have found retreatment rates comparable to those presented. Willcox reported retreatment rates of 14.8 percent at the end of 3 months in a group of white patients treated with an oral penicillin preparation (*2*). Dallas reported a treatment failure rate of 14.1 percent at 3 months in a series of 447 male patients treated with 300,000 units of procaine penicillin at St. Thomas Hospital, London (*3*).

Our data show that the use of benzathine penicillin in the therapy of acute gonorrhea in men offers no discernable long-term advantage to our gonorrhea control program. There are, we believe, several disadvantages to the use of this agent.

The most obvious disadvantage is the added cost of therapy with benzathine penicillin. It is several times that of an equivalent unitage of procaine penicillin with 2 percent aluminum monostearate in oil, for instance.

Figure 3. Cumulative retreatment rates for 3,622 male gonorrhea patients in 16 weeks following therapy, Houston, 1954–59



Another and very considerable disadvantage to the use of benzathine penicillin is the persistent discomfort at the site of injection. This pain we believe to be severe enough to inhibit the patient's return to the clinic should he become reinfected. Perhaps the short-time failure rate is actually the same with all schedules, but the recent memory of persistent discomfort of the benzathine penicillin injection inhibits the return of patients who are treatment failures until, with passage of time, memory of pain fades while persistence of symptoms becomes worrisome enough to stimulate their return. This factor could well contribute to the "antibiotic quarantine." In addition, we suspect the associated pain may well drive our patients to sources of therapy, both legal and illegal, where no epidemiology is carried out.

We find that use of benzathine penicillin in men often tends to confuse the epidemiological picture in gonorrhea control. Most of our male clinic patients are aware of the short incubation period of the disease, but unaware of the period of antibiotic quarantine provided by the drug. When the patient returns to his unnamed, untreated, and still infected sex partner and is not almost immediately reinfected, he assumes her free of the disease. When reinfection does ultimately occur, he is unable to associate his reinfection with its actual source. Under these circumstances, patients are not easily persuaded to reveal the identity of their sex partners to the epidemiological investigator.

The chances for the development of penicillin-resistant strains of gonococci would seem to be enhanced when long-acting penicillin is given to promiscuous persons who are members of a socio-sexual group having a high gonorrhea prevalence. When persons with persisting low levels of penicillin in their blood are repeatedly exposed to numerous sexual partners, and consequently to varying strains of gonococci, it is likely that organisms which are penicillin resistant will eventually be selected. Such a situation would essentially reproduce the cultural conditions that are used in the laboratory to produce drug-resistant bacteria. Since there appears to be a theoretical possibility of promoting the evolution of

populations of drug-resistant organisms, this seems to us to be an added reason for not using the agent.

We have discussed several disadvantages to the use of long-acting penicillin in acute gonorrhea in men. The disadvantages, while considerable, might be tolerated if the use of long-acting penicillin provided compensating advantages in the control of gonorrhea. In Houston we have not been able to show any influence on gonorrhea morbidity, or in long-term retreatment rates through the use of this agent in men. We have, therefore, discontinued its use in men coming to our clinic with gonorrhea.

We are continuing to give long-acting penicillin to women. Takos and co-workers have formulated an epidemiological rationale for such therapy based on the differences in the natural history of the disease in men and women (*4*). In the vast majority of women, gonorrhea is asymptomatic, or nearly so, and they do not usually seek treatment voluntarily. For these reasons, the objective of the therapeutic schedule followed by these researchers is to cure the patient of her Neisserian infection and at the same time protect her from reinfection for about 6 weeks. In addition, Garson and Barton have recently discussed theoretical therapeutic advantages of treating gonorrhea in women with long-acting penicillin (*5*).

The therapeutic schedule used by Takos and co-workers in men was founded upon three assumptions: (*a*) the promiscuously exposed male urethra is the most effective casefinding tool known, (*b*) when a man becomes infected, he will be symptomatic, and (*c*) his symptoms will cause him to seek medical attention. Takos' male patients were treated with enough short-acting penicillin to effect a rapid cure, but care was taken not to give long-acting penicillin, with its resultant several weeks of antibiotic quarantine. The cured but still promiscuous man is swiftly returned to risk in his high-gonorrhea-incidence social milieu. His active libido and minimal inhibitions are thus utilized again and again to locate additional asymptomatic but infected women.

Summary

Four different penicillin schedules were used in the therapy of acute gonorrhea in 3,622 men at the venereal disease clinic, Houston, Tex. The objective was to determine what effect the use of benzathine penicillin might have on the gonorrhea control program in Houston.

Patients treated with a mixture of long- and short-acting penicillin showed lower retreatment rates for gonorrhea during the first 4 weeks of the followup period. This was presumably due to an antibiotic quarantine against reinfection, resulting from the prolonged action of the benzathine penicillin. In the next 12 weeks of the followup period, it was found that those patients treated with mixtures containing long-acting drugs returned with gonorrhea at a faster rate than did those treated originally with a single drug. At the termination of the full 16 weeks' followup period, there was no appreciable difference in the cumulative retreatment rate on any of the schedules.

No correlation could be shown between the use of any treatment schedule and changes in gonorrhea morbidity at our clinic in Houston.

No long-term advantage to gonorrhea control could be demonstrated through the use of benzathine penicillin in the therapy of acute gonorrhea in men.

Several disadvantages, both practical and theoretical, to the use of long-acting penicillin in men with acute gonorrhea are discussed.

REFERENCES

(*1*) Hookings, C. E., and Graves, M. L.: Benzathine penicillin G in the control of gonorrhea. Brit. J. Ven. Dis. 33: 40–42, January 1957.

(*2*) Willcox, R. R.: Oral penicillin for gonorrhea: Some experiences with phenoxymethyl penicillin (penicillin V) in white and Negro patients. Brit. J. Ven. Dis. 34: 118–121, June 1958.

(*3*) Dallas, N. L.: Penicillin treatment failures in male gonorrhea. Brit. J. Ven. Dis. 34: 194–195, September 1958.

(*4*) Takos, M. J., Elgin, L. W., and Cato, T. E.: Long-acting penicillin in gonorrhea control. Pub. Health Rep. 72: 976–980, November 1957.

(*5*) Garson, W., and Barton, G. D.: Problems in the diagnosis and treatment of gonorrhea. Pub. Health Rep. 75: 119–123, February 1960.