

Long-Acting Penicillin in Gonorrhea Control

MICHAEL J. TAKOS, M.D., M.P.H., LEE W. ELGIN, M.D., and T. ELAM CATO, M.D., M.P.H.

PREVENTION of the spread of gonorrhea from one person to another is one of the most difficult problems in venereal disease control. Individuals acquiring gonorrhea can spread the disease after only a brief incubation period. Unlike syphilis, there are no long periods when it is virtually impossible to transmit the disease.

The principal factor behind the difficulty in controlling gonorrhea is that the infected female is usually completely unaware that she has an infectious disease. Unpublished studies of 318 women with laboratory proved diagnoses of gonorrhea infection at the Dade County Venereal Disease Control Clinics showed that only 22 (6.9 percent) came to the clinics because they themselves were aware that they were infected. Of this group, 12 reported on questioning that they did not know they had this disease until they were so informed by their latest sexual partners. Thus, only 10 females, or 3.1 percent of the group studied, had developed symptoms of sufficient severity to cause them to seek medical assistance. In contrast, of 711 males

studied, 701, or 98.6 percent, came into the clinics voluntarily because they knew they were infected.

Adding to the difficulties of gonorrhea control is the fact that our present laboratory methods of demonstrating neisserian infection in the female by smear and culture techniques are not very effective. Furthermore, the clinical diagnosis of uncomplicated gonorrheal infection in the female is quite difficult. Thus, the male urethra still remains the most effective culture and diagnostic medium known for indicating which women in the population are harboring the gonococcus.

Methods

Consideration of these epidemiological facts led to a change in the gonorrhea control program of the venereal disease control clinics in an attempt to decrease the the rate of spread of the disease in Dade County, Fla.

All female contacts of male gonorrhea patients at the clinics who came within the jurisdiction of the health department were treated with 2.4 million units of benzathine penicillin G (Bicillin). This dosage was given in divided doses of 4 cc. (1.2 million units) in each buttock. Studies by various investigators have shown that this procedure allows the maintenance of effective therapeutic blood levels of penicillin for at least 6 weeks (1-3). The objective of this therapy was to cure the patients of their neisserian infection, and, at the same time, to protect them from reinfection by the gonococcus for approximately 6 weeks. Thus, we would create an interlude during which women al-

This paper is a joint contribution of the Dade County Health Department and the section of preventive medicine, University of Miami School of Medicine, Miami, Fla. The authors are all members of the Dade County Health Department. Dr. Takos, formerly head of the venereal disease control division, is now in charge of the research and special studies division; Dr. Elgin is the present head of the venereal disease control division; and Dr. Cato is the health commissioner. Dr. Takos and Dr. Cato are also instructors in preventive medicine, University of Miami School of Medicine.

readily known to have been infected would not be able quickly to reacquire the disease and so continue to spread it in the community. It seemed reasonable to assume that those women who already had gonorrhoea were those most likely to get it again. This assumption is borne out by the data from our studies of 318 women with neisserian infections. Of this group, 93 (29.2 percent) had previous diagnoses of gonorrhoea infection on the clinic records.

In the clinics, we continued to treat male gonorrhoea patients with the previously used standard therapy of 600,000 units of 72-hour repository penicillin (aqueous procaine penicillin G with aluminum monostearate). This had been our standard therapy in the past for both males and females. The males were cured within a week and could be reinfected by the gonococcus as soon as the therapeutic blood level of penicillin disappeared. Our objective was to continue using the males as a medium through which to find the infected female reservoirs of neisserian disease in the population. Possibly the total number of individuals infected with the gonococcus could have been sharply reduced by using Bicillin therapy for both males and females since nearly 44 percent of our male patients become reinfected in less than 6 months. But this technique would also have eliminated the best method now available for locating females with gonorrhoea.

Table 1. Total laboratory-proved gonorrhoea cases treated at Dade County, Fla., clinics, 1953-56

Month	1953	1954	1955	1956
January	142	194	147	119
February	118	200	108	122
March	143	196	133	114
April	165	177	128	108
May	167	155	127	145
June	186	¹ 159	149	112
July	196	146	129	148
August	169	152	168	128
September	158	137	156	118
October	178	165	136	162
November	172	160	127	89
December	185	121	126	99
Total	1,979	1,962	1,634	1,464
Mean cases per month	164.9	163.3	136.1	122.0

¹ Benzathine penicillin program started.

Table 2. Total gonorrhoea cases in Florida metropolitan areas before and after period of use of benzathine penicillin in Miami, January 1954-February 1955

Month	Miami	Jacksonville	Tampa
Prior to benzathine penicillin program			
<i>1954</i>			
January	171	99	67
February	163	78	67
March	119	92	94
April	182	83	103
May	163	120	73
Total cases	798	472	404
Mean cases per month	159.6	94.4	80.8
After benzathine penicillin program			
June	115	110	80
July	113	72	112
August	115	156	62
September	123	107	87
October	170	128	119
November	117	71	64
December	138	178	73
<i>1955</i>			
January	103	56	65
February	104	158	72
Total	1,098	1,036	734
Mean cases per month	122.0	115.1	81.6

The Bicillin program was begun in June 1954 at all of the venereal disease control clinics in Dade County. During the first 2 months, smears and cultures were run once a week for 3 weeks on the females treated with Bicillin to check the effectiveness of the method. Of 48 women whom we were able to follow for 3 successive weeks, none had positive smears or cultures. Hookings and Graves (4) have reported similar results from their studies in Tennessee.

In Dade County, we use a modified "speed-zone" system of epidemiological tracing of the contacts of gonorrhoea patients; because of the highly mobile nature of our population, we do not discontinue contact tracing until several months after a contact is first reported. Other than the use of benzathine penicillin, the only new factor added to our routine is a firm policy of refusing to treat male gonorrhoea patients with long clinic records who would not or had

not furnished us with the names of traceable female contacts. However, this procedure had been in unofficial use for some time prior to June 1954. We reported to the central registry unit of the Florida State Board of Health all cases diagnosed but not treated.

Results

Once the program had a good start, we expected to see a falling off of the number of proved gonorrhea cases treated at the venereal disease control clinics. Proved gonorrhea cases are those having either positive smears or cultures, or both. Female contacts of males with gonorrhea are not considered cases unless positive laboratory evidence is obtained. This expectation was promptly borne out by the total number of proved gonorrhea cases coming to therapy at the clinics (table 1). The first 6 months of 1954 averaged 180.1 cases of gonorrhea per month treated at the clinics, while the last 6 months averaged only 146.8 cases per month. So a decrease in the number of cases of gonorrhea did occur shortly after benzathine penicillin began to be used and has continued during succeeding years.

One factor which had to be considered was the possibility that the evident decrease in the number of gonorrhea cases was artificial due to some statistical factor other than the Bicillin program. To help eliminate serious consideration of this point, the venereal disease control regis-

try unit of the Florida State Board of Health was asked to send us all monthly records of gonorrhea cases reported by clinics and private practitioners from within the city limits of Miami, Jacksonville, and Tampa, the three largest metropolitan centers in the State. Benzathine penicillin was not used in the venereal disease clinics in Jacksonville or Tampa during the period for which data are presented in table 2. These data show a marked falling off in the incidence of gonorrhea cases in the Miami area during a period when the incidence became higher in Jacksonville and showed no significant change in Tampa. These figures have been checked through Student's *t* test and are significant (table 3).

The best indication of the effectiveness of a control program is its effects on the community rates for the disease in question. Table 4 presents the data on total gonorrhea cases reported from Dade County at venereal disease clinics and by private practitioners and gives the estimated permanent population of the area and the gonorrhea morbidity rates. The morbidity rate was 2.1 per 1,000 in 1956 and averaged 3.1 during 1952, 1953, and 1954. If the average rate for 1956 had been 3.1 per 1,000, we should have had 2,276 cases of gonorrhea rather than the 1,554 actually reported.

Another possible source of distortion of these data would be selective treatment of females by deliberately searching them out. This might result in a rate higher than that usually ob-

Table 3. Standard error of the difference of the means and probability of the data in table 2

	Miami	Jacksonville	Tampa
Standard error of mean difference.....	12.8	22.7	19.8
Student's <i>t</i>	2.9	0.9	0.04
Probability	0.02 > p > .01	p > 0.05	p > 0.05
Meaning	Significant 1:50 > p > 1:100	Not significant	Not significant

Small sample method (Student's *t*): Null hypothesis: the two samples are drawn from populations identical both as to mean and variance.

$$\text{Pooled estimate of variance } \hat{\sigma}^2 = \frac{n_1 s_1^2 + n_2 s_2^2}{n_1 + n_2 - 2}$$

$$\text{Standard error for the difference of the means } \hat{\sigma}_w = \hat{\sigma} \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

$$t = \frac{[\bar{x}_1 - \bar{x}_2]}{\hat{\sigma}_w}$$

SOURCE: Moroney, M. J.: Facts from figures. Rev. ed. Baltimore, Penguin Books, 1954, p. 227 and seq.

Table 4. Total gonorrhea cases, population, and gonorrhea morbidity rates, Dade County, Fla., 1952-56

Year	Total reported cases	Estimated population ¹	Rate per thousand
1956.....	1, 554	734, 142	2. 1
1955.....	1, 663	703, 777	2. 4
1954.....	2, 030	658, 460	3. 1
1953.....	1, 994	617, 616	3. 1
1952.....	1, 808	576, 772	3. 1

¹ As calculated by vital statistics division, Dade County Health Department.

tained. Data from the Dade County clinics show that this has not occurred. During 1953, 30 percent of the proved gonorrhea cases were in females. This proportion of females to the total number of cases has varied between 30 and 35 percent during the entire period covered here. One other factor, not previously mentioned, was the possible effects of a shift in the population of this area toward a greater proportion of white than Negro residents. Since our clinic records show a ratio of 9 Negroes to 1 white with gonorrhea, any decrease in the proportion of Negroes in the resident population might well be expected to account for a decrease in gonorrhea rates. This has not occurred. In 1953, 13.1 percent of the resident population were Negroes; in 1956, 13.9 percent. Hence a decline in the gonorrhea rates took place during a period when the proportion of Negroes in the population showed a slight increase.

Treatment Failures

There have been six instances of treatment failure in females. Treatment is considered to be a failure when the female is reported as transmitting gonorrhea during a period within 6 weeks after receiving benzathine penicillin. In two of these cases, searching inquiry into dates of exposure showed that the patients had become infected and had transmitted the disease during the seventh week after receiving benzathine penicillin. One woman supposedly infected a sailor about 4 weeks after receiving benzathine penicillin. She was examined about a week later, and repeated smears and cultures were negative for gonococcus. This woman was

a prostitute and had had sexual congress with at least three customers during the same evening in which infection probably occurred in the sailor, who denied other exposure. It is possible that the man may have been infected by discharges of the other customers remaining in the vaginal vault. We do not know what happened in the other three cases, except that the infection was transmitted during the fifth week following benzathine penicillin therapy. Perhaps these women excreted penicillin faster than others or somehow failed to obtain the total dosage.

Discussion

A steady decline in the total incidence of gonorrhea in the Dade County area occurred after initiation of the program of using benzathine penicillin for the treatment of gonorrhea in females. Data are presented showing a reduction in the total numbers of infected persons coming to the venereal disease control clinics and in the general gonorrhea morbidity rates for the community. The number of cases declined in Miami during a time when the number of cases was not decreasing in other metropolitan areas of Florida.

The use of benzathine penicillin apparently creates a period when reinfection becomes virtually impossible for the female. It is also possible that long-acting penicillins may be more effective than our previously used therapy in obtaining a complete cure in the female with neisserian infection. Either or both of these explanations may be operating, but we do not have sufficient evidence to prove this point. Males are treated with short-acting penicillin in order that they may be used for locating gonorrhea-infected women in the population. Satisfactory results were obtained in the Dade County area, even though we used a modification of the "speed zone" epidemiology method of contact tracing.

To be effective, the long-acting penicillin method requires that a fairly large proportion of infected women be brought to treatment. In Dade County we locate nearly half of our proved female gonorrhea cases by routine smear and culture examinations of women and girls in the local jails, of health card applicants, and

of individuals coming to county maternity centers. Only about 35 percent of our laboratory-proved cases of gonorrhea in females are found through contact tracing. Female contacts of men with gonorrhea are treated with benzathine penicillin but are not counted as gonorrhea cases unless the diagnosis is confirmed by the laboratory studies.

It is hard to assay any difficulties produced by a drug in those who receive it. The massive doses of benzathine penicillin used in our clinics apparently did not produce any more allergic reactions in patients than did the smaller doses of short-acting penicillins. There were many complaints of pain in the buttocks after injection, and an occasional individual had some difficulty in walking after Bicillin therapy. None of these effects lasted more than 24 hours, and those affected were usually the highly excitable individuals.

Long-acting penicillin certainly does not offer a panacea for the immediate elimination of gon-

orrhoea from a population. But it does offer a possibility for a slow, steady decline which may eventually decrease the numbers of infected individuals to a point where the disease can be considered to be effectively controlled.

REFERENCES

- (1) Putnam, L. E., and Roberts, E. F.: Prolonged blood concentrations of penicillin following intramuscular benzathine penicillin G. *Antibiotics* 4: 931-933, September 1954.
- (2) Smith, C. A., O'Brien, J. F., Simpson, W. G., Harb, F. W., and Shafer, J. K.: Treatment of early infectious syphilis with N,N'-dibenzylethylenediamine penicillin G. *Am. J. Syph., Gonorr. & Ven. Dis.* 38: 136-142, March 1954.
- (3) Stollerman, G. H., and Rusoff, J. H.: Prophylaxis against group A streptococcal infections in rheumatic fever patients. Use of a new repository preparation. *J. A. M. A.* 150: 1571-1575, December 20, 1952.
- (4) Hookings, C. E., and Graves, L. M.: Speed zone epidemiology: A preliminary report on benzathine penicillin G for gonorrhoea in women. *Pub. Health Rep.* 71: 1142-1143, November 1956.

Advisory Group on Medical Research and Education

A group of special consultants have been appointed by the Secretary of Health, Education, and Welfare to advise him on the status and future needs of medical research. The consultants will investigate such questions as the impact of the expanding research programs on medical education, the availability of scientists, technicians, and facilities, and the relative emphasis on research in the various disease fields. Other subjects to be studied are the relative emphasis given to fundamental studies in the basic sciences generally, the relationship between Federal and private research programs, and the standards for approval of research projects.

Chairman of the group is Dr. Stanhope Bayne-Jones, former dean of the Yale Medical School, and more recently presi-

dent of the New York Hospital-Cornell Medical Center Joint Administration Board and technical director of research in the Army Medical Research and Development Program. Other members are:

Dr. George Packer Berry, dean, Medical School, Harvard University; Thomas P. Carney, vice president, Eli Lilly & Co.; Dr. Lowell T. Coggeshall, dean, division of biological sciences, University of Chicago.

Fred Carrington Cole, vice president, Tulane University; Samuel Lenher, vice president, E. I. du Pont de Nemours Co.; Dr. Irvine H. Page, director of research, Cleveland Clinic Foundation; Robert C. Swain, vice president in charge of research and development, American Cyanamid Co.

Dr. Stafford L. Warren, dean, School of Medicine, University of California Medical Center; and James Edwin Webb, president and general manager, Republic Supply Co. (former Under Secretary of State and former Director of the Bureau of the Budget).