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Comparative Study of Two Therapies for Gonorrhea

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PENICILLIN has lost some of its once devastating effectiveness against *Neisseria gonorrhoeae*: more and more strains have become relatively resistant during the past decade (*1*). Gonorrhea now contracted by U.S. servicemen in the Far East, particularly in Vietnam, is reported as often resisting treatment (*2–4*).

Such resistant organisms spread rapidly among the civilian population, and the Alameda County Health Department venereal disease clinic in Oakland, a port of debarkation from Vietnam, inevitably acquired an influx of patients who failed to respond to the standard therapeutic regimen. The standard regimen was 1.2 million units of aqueous procaine penicillin G (APP) plus 1.2 million units of the more slowly released and longer acting aqueous procaine penicillin G with 2 percent aluminum monostearate (PAM).

To counter the threat of penicillin resistant gonococci, clinicians began to omit the PAM and to increase the dose of APP to the level recommended since 1965 by the Food and Drug Administration and the Public Health Service and subsequently adopted by the joint U.S. military forces. This schedule consists of a single intramuscular injection of 2.4 million units of APP in men and 4.8 million units in women (*5,6*).

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Broad-spectrum antibiotics were rejected for our purpose, since none are suitable for use in public health venereal disease clinics, where a single visit from the patient is generally the most that can be expected. Some broad-spectrum antibiotics are otherwise acceptable alternatives to penicillin for therapy of gonorrhea (*3,7,8*). All broad-spectrum drugs so far developed generally are more toxic than penicillin, and most require oral administration. The patient is responsible for continued medication when orally administered drugs are prescribed, and the patient is often undependable.

Tetracycline, an excellent antigonococcal agent, is especially effective in treatment of postgonococcal urethritis (*9*). Nevertheless, laboratory studies indicate a growing resistance of *N. gonorrhoeae* to tetracycline (*1, 10, 11*). Therefore, tetracycline should be reserved for treating the penicillin-hypersensitive patient and for combating gonococci known to be resistant to penicillin.

This study was undertaken to determine if penicillin can still be given in a single intramuscular dose large enough to produce serum levels adequately bactericidal for all *N. gonorrhoeae*, including strains passed along from servicemen returning from Vietnam. The dosage levels recommended by the Food and Drug Administration and the Public Health Service were adopted. Rigid criteria were imposed to distinguish reinfections from treatment fail-

ures. The results indicated that the Food and Drug Administration and the Public Health Service regimen is adequate in women but that the dose for men may have to be increased.

Methods and Materials

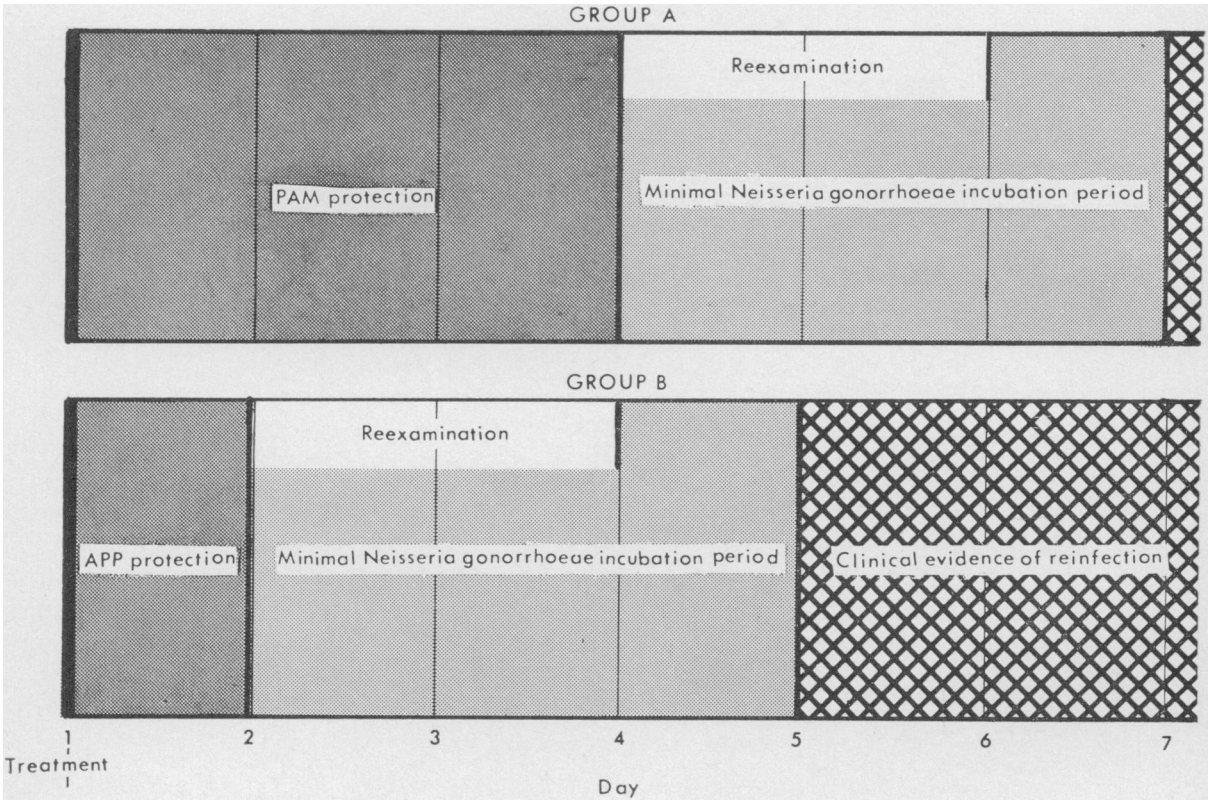
Group A patients were treated according to the old dosage schedule of APP and PAM, the same dose being given to both men and women. Group B patients received the increased dosage recommended by the Food and Drug Administration and the Public Health Service (2.4 million units of APP in men and 4.8 million units in women). The APP was administered with a 4-cc., 2,400,000-unit, single-dose, disposable syringe (*A*). All doses were administered intramuscularly in one session.

Gonorrhea was diagnosed positively by laboratory methods. The presence of *N. gonorrhoeae* was objectively demonstrated in all patients by a smear of exudate from men and by culture of the vaginal discharge (specimen from cervix and urethra) from women. Women named as contacts were included in the study only if they came voluntarily to the clinic.

Patients were assigned randomly to the two treatment groups. A total of 251 patients was treated in group A, but only 106 (83 men and 23 women) returned for followup and could thus be evaluated. Similarly, 232 patients started in group B, but only 119 (98 men and 21 women) remained in the study. The difference of 19 patients between group A and B (251 and 232) was attributed to penicillin allergy and, therefore, these 19 were deleted from the study. The study period was from October 20, 1967, through February 2, 1968. The tight reexamination schedule necessitated exclusion of all patients who missed appointments.

At the reexamination, specimens for culture were obtained from both women and men. Groups A and B were reexamined at different intervals: group B between the second and fourth days after treatment, and group A between the fourth and sixth. As shown in the chart, all APP is eliminated from the body in about 24 hours, while PAM may be retained for

Chronology of gonorrhea infection and treatment rationale



up to 72 hours. (This permits PAM to maintain a low blood level concentration, which may permit a degree of protection from reinfection in some persons).

The incubation period for *N. gonorrhoeae* usually ranges from 3 to 4 days. Reinfections occurring after the period of penicillin protection (1 to 3 days) would not become clinically evident until 5 days after treatment of patients in group B and 7 days after treatment of patients in group A.

Treatment was considered a failure if, when the patient was reexamined, there was laboratory evidence of persisting *N. gonorrhoeae*. These patients were retreated in accordance with the higher dosage of the group B regimen.

Results

As shown in table 1, 4.8 million units of APP were curative in all women, but 2.4 million units were inadequate in some of the men. Specifically, the fast-acting APP produced a distinctly higher cure rate in both sexes: 92 percent compared with 77 percent for APP plus PAM, a difference that is statistically significant at the $P<0.01$ level by chi-square tests (table 2). The difference in men in group A and men in group B, while considerable, was not large enough to be statistically significant (tables 1 and 2). (Yates' factor was used in the computations. This procedure prevented false rejections of the valid hypothesis by changing the frequency in each cell by 0.5 without changing marginal totals). No hypersensitivity or other adverse reaction was noted.

Discussion

It is difficult to evaluate agents for use in a public health venereal disease clinic. Drugs that require oral administration are apt to be poorly absorbed.

Although erratic absorption can be overcome by giving larger and more frequent doses, few patients can be relied on to take all the tablets

Table 1. Comparison of 2 single-dose penicillin regimens for treatment of gonorrhea

Regimen and sex	Entered study	Completed study [1]	Cured		Treatment failures	
			Number	Percent	Number	Percent
APP and PAM [2] (both sexes)	251	106	82	77	24	23
Men	212	83	68	82	15	18
Women	39	23	14	61	9	39
APP [3] (both sexes)	232	119	110	92	9	8
Men	198	98	89	91	9	9
Women	34	21	21	100	0	0

[1] Patients who did not keep appointments for reexamination were lost to followup.
[2] 1.2 million units of aqueous procaine penicillin G plus 1.2 million units of aqueous procaine penicillin G with 2 percent aluminum monostearate. The same dose was given to men and women.
[3] 2.4 million units of sterile procaine penicillin G suspension for men and 4.8 million units for women.

Table 2. Results of chi-square tests applied to cure rates (table 1 data) with 2 treatment regimens

Compared groups	Uncorrected value	Corrected value [1]	Probability value (P)	
			Lower limit	Upper limit
Men receiving APP and PAM with those receiving APP	3. 09		0. 25	[2] 0. 10
Women receiving APP and PAM with those receiving APP		5. 21	. 01	. 05
Patients (both sexes) receiving APP and PAM with those receiving APP	10. 18		. 001	. 01

[1] Using Yates' factor because 1 of the expected frequencies was less than 5.
[2] Not significant.

or capsules prescribed. Once the more distressing aspects of gonorrhea have disappeared, there is a strong temptation to neglect further medication.

Many patients do not return to the clinic unless symptoms persist or recur. One might assume that not returning to the clinic implies cure, since the symptoms of full-blown gonorrhea are tolerated poorly by the average male. Yet gonococci may survive without producing symptoms, or the disease may become chronic and produce milder, less distressing symptoms, or the patient, even if not cured, may go elsewhere for treatment.

Evaluating treatment without due regard for the incubation period of *N. gonorrhoeae* and the period of protection afforded by penicillin may cause investigators to fail to distinguish clearly between ongoing infections and reinfections. In this study, an attempt was made to surmount the difficulties of evaluation by employing a single intramuscular injection and by judging the results strictly on the basis of bacterial culture.

The results indicate that gonorrhea is still adequately responsive to sufficiently high levels of penicillin, but that the dosage may have to be increased even beyond the presently recommended level in men, or that probenecid may have to be given adjunctively to maintain the serum peaks for a longer period. Antimicrobial agents other than penicillin have given cure rates not substantially different from those reported in this paper. Seldom do investigators obtain more than 92 percent cures, and rare indeed has it been to achieve the 100 percent success as obtained in the women of this study.

The search for suitable substitutes for penicillin must certainly continue, particularly in view of the constantly changing patterns of microbial resistance (*12–15*). Until good substitutes are found, it is comforting to realize that penicillin has not lost its efficacy in such basic, straightforward applications as gonorrhea. Available evidence suggests that increased dosage of procaine penicillin G suspension should suffice to eradicate gonococci now encountered (*4*, *10*). However, this proposition should be continuously retested, if possible, using much larger groups of patients than could be assembled for this study.

Summary

The aqueous procaine penicillin G (APP) regimen recommended for treatment of gonorrhea by the Food and Drug Administration and the Public Health Service was compared with a lower dose regimen of APP plus PAM (penicillin with aluminum monostearate) in 225 patients at the Alameda County Health Department venereal disease clinic in Oakland, Calif., a port of debarkation from Vietnam.

The cure rates, as determined by culture, were 77 percent for the 106 patients in group A (all of whom were given 1.2 million units of aqueous procaine penicillin G plus 1.2 million units of aqueous procaine penicillin G with 2 percent aluminum monostearate) and 92 percent for the 119 in group B (the Food and Drug Administration and the Public Health Service regimen); the difference was statistically significant at the $P<0.01$ level by chi-square test.

The 21 women of group B, who received 4.8 million units of procaine penicillin G suspension instead of the 2.4 million units given the men, were all cured. The men of this group had a higher cure rate than the men of group A, but the difference was not statistically significant. No adverse reactions were noted. Results indicated that gonorrhea can still be effectively treated by a single intramuscular injection of a sufficiently large dose of fast-acting penicillin.

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SUPPLY REFERENCE

(A) Wycillin®, Wyeth Laboratories, P.O. Box 8299, Philadelphia, Pa. 19101.

Tearsheet Requests

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Computers in Medical Education

A self-instruction program using computers that will allow the student to study at his own pace is being developed through the award of a $1,400,000, 3-year grant from the Division of Physician Manpower, National Institutes of Health, to the Ohio State University College of Medicine.

Under the direction of three medical educators and a systems analyst at the College of Medicine, the theory that independent study can improve the efficiency of medical education will be tested. Findings of the experiment such as newly developed teaching concepts, techniques, and materials will be released for use by other medical schools.

A key aim of this project is to overcome a major weakness of the present lockstep method of instruction which compels students to advance at the same pace. All students do not arrive at medical schools with the same degree of preparation for various medical subjects. Moreover, they vary as to their intellectual capability, interest, study habits, personalities, and backgrounds.

The major advantage of the self-instruction project is that it recognizes these differences among students and attempts to tailor the teaching schedule to the individual student rather than fit all students to a common program. Because this demonstration may help minimize student dropouts, it is significant implications for this country's future supply of physicians.