Evaluation of Tetracycline Phosphate Complex *and* Other Antibiotics *in* Treatment of Gonorrhea in Males

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DURING the 18-month period from March 1960 through August 1961, approximately 4,400 cases of acute gonorrheal urethritis in male patients were treated at the Fulton County Health Department, Atlanta, Ga., on research schedules using 11 different antibiotic preparations. This report includes 18 schedules, with the number of patients treated on each schedule ranging from 50 to 505.

The pretreatment diagnosis, as well as determination of treatment failure, was based on clinical evidence of gonorrhea plus a stained smear showing intracellular gram-negative diplococci resembling *Neisseria gonorrhoeae*. Because of the large number of patients treated at the health department, confirmation by isolation culture and specific sugar fermentation studies was impossible. However, in a sample group of 75 such positive patients confirmation was obtained in 95 percent by specific fluorescent antibody identification or by fluorescent antibody identification plus isolation culture and sugar fermentation. We believe, therefore, that the cases treated and included in this evaluation represent gonococcal infections and do not include a large proportion of nonspecific urethritis which would respond more readily to the broad-spectrum antibiotics.

Patients were instructed to report to the clinic for post-treatment examination 2 to 4 days after treatment, depending upon the day of the week treatment was administered. If patients failed to return as requested, a follow-up letter or telegram was sent. Fifty-three percent of the patients returned to the clinic within a 2-week period following treatment.

Failure to obtain 100 percent post-treatment observation raises the question of the proper base to be used for calculating failure rates. Either of two assumptions can be made:

1. That all patients will return if treatment has been unsuccessful. The total number of patients treated would then be used. On this basis, the overall failure rate in this series would be 9.7 percent.

2. That patients who return for observation are not different from patients who do not return for observation. The number of patients observed would then be used as the base, which would result in this series in a failure rate of 18.3 percent.

We felt that the first assumption was more

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nearly correct. However, to support this hypothesis, 34 patients were given placebo consisting of an intramuscular injection of distilled water. Eighty-five percent of these patients returned to the clinic within 1 week, and 91 (±10.0) percent within 2 weeks following the injection. All those returning were still positive for gonorrhea. Applying the experience in the placebo group to treatment failure cases, the observed failure rate of 9.7 (± 0.9) percent would represent 91 percent of the true failure rate, or 10.7 percent. Since the difference between the observed rate and the adjusted rate is so slight and because the adjustment factor would be the same for all schedules of treatment, no attempt has been made to adjust the failure rate for the individual schedules.

Also, no attempt has been made to differentiate between treatment failure and reinfection, other than by limiting followup to 2 weeks, which arbitrarily classifies patients returning later as reinfections. Epidemiologic information, however, indicates that approximately one in five of the patients re-treated within 2 weeks following treatment represents reinfection.

Figure 1. Comparison of various types of penicillin in the treatment of gonorrhea in males

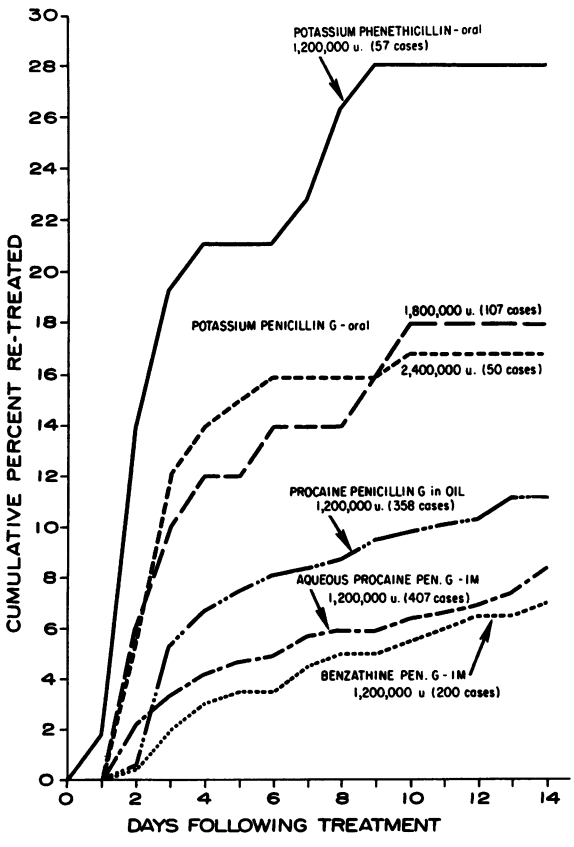
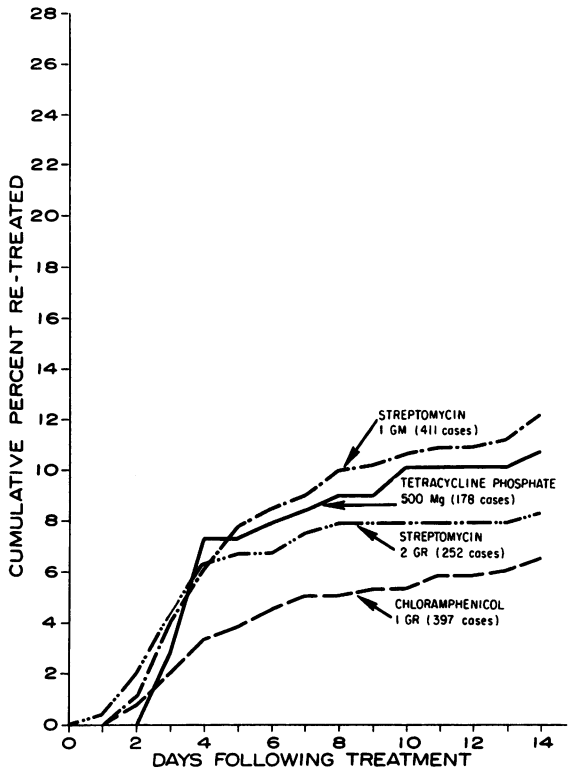


Figure 2. Single intramuscular injection of antibiotics other than penicillin, in treatment of gonorrhea in males



The 11 antibiotics evaluated included 5 penicillin preparations, 3 intramuscular and 2 oral. The three intramuscular preparations were administered in a single 1,200,000-unit injection. One oral preparation, potassium penicillin G, was given in two schedules, 3 doses of 600,000 units each at 6-hour intervals for a total of 1,800,000 units and 6 doses of 400,000 units each at 4-hour intervals for a total of 2,400,000 units. The other oral preparation, potassium phenethicillin, consisted of a total dosage of 750 mg. (1,200,000 units) given in two doses of 375 mg. each, with a 12-hour interval between. A comparison of these schedules is shown in figure 1.

In the dosages employed, the intramuscular penicillin preparations proved superior to the oral, with aqueous procaine penicillin G and benzathine penicillin G giving the best results. Although the high failure rate following treat-

ment with potassium phenethicillin discouraged its use, 11 additional patients were treated with 3,200,000 or 4,800,000 units given in doses of 400,000 and 800,000 units, respectively, at 4-hour intervals, with little or no improvement in results.

Three intramuscular preparations other than penicillin were evaluated; chloramphenicol, streptomycin, and tetracycline phosphate. As shown in figure 2, 1 gram of chloramphenicol appears superior to 2 grams of streptomycin and to 500 mg. of tetracycline phosphate. Unfortunately, larger single doses of chloramphenicol are not recommended. Although the oral administration of chloramphenicol has reportedly resulted in rare blood dyscrasias, there have been no reports of similar effect from parenteral chloramphenicol.

Two of the oral preparations evaluated, erythromycin and triacetyloleandomycin, are compared in figure 3. When administered in a

Figure 3. Various oral schedules of erythromycin and triacetyloleandomycin in treatment of gonorrhea in males

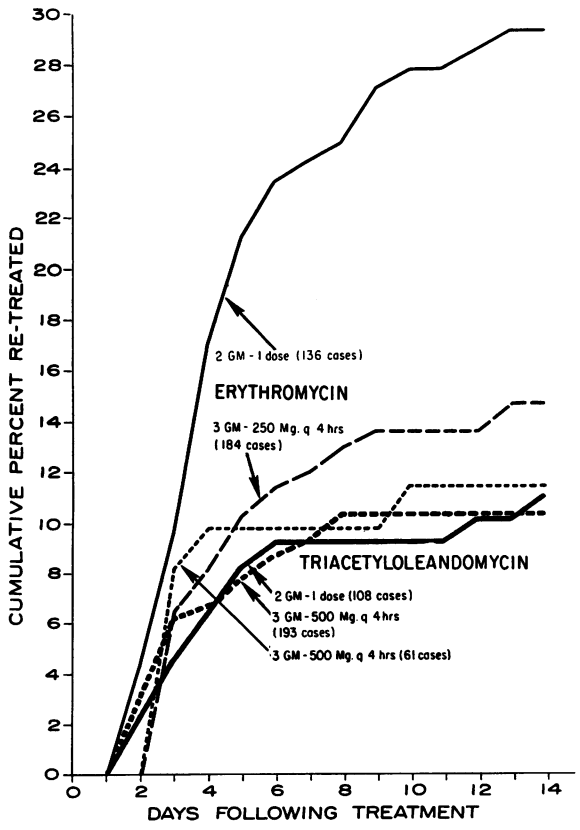
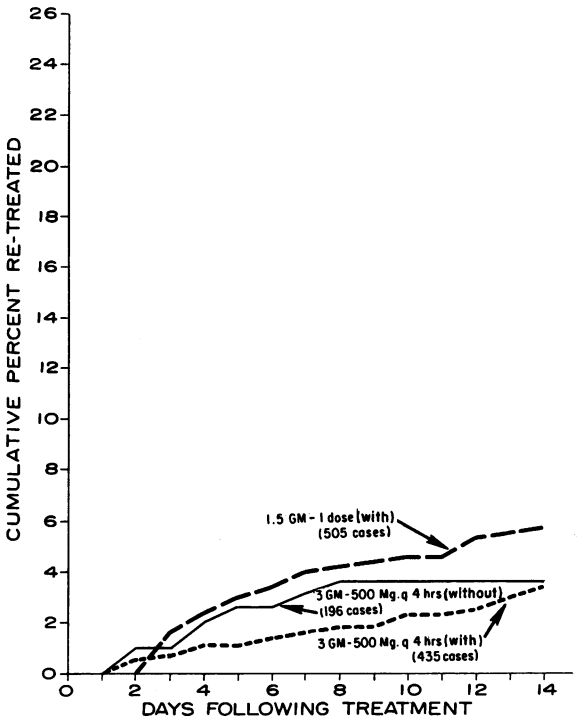


Figure 4. Oral phosphate potentiated tetracycline, with and without amphotericin B, in treatment of gonorrhea in males



single 2-gram dose, triacetyloleandomycin was far superior to erythromycin. Similar results were obtained with the two drugs, however, when administered in divided doses of 500 mg. every 4 hours for a total of 3 grams. Unlike erythromycin, 2 grams of triacetyloleandomycin in a single dose was just as effective as 3 grams given in divided doses over a 20-hour period. For even the best schedules of these two drugs, however, the cumulative failure rates range between 10 and 12 percent at 14 days following treatment.

The most promising drug included in the evaluation, also an oral preparation, was phosphate potentiated tetracycline. The form initially used included amphotericin B. The outstanding results obtained with 3 grams given in divided doses of 500 mg. every 4 hours prompted further investigation. Each capsule of this preparation contains tetracycline phosphate complex equivalent to 250 mg. of tetracycline hydrochloride and 50 mg. of amphotericin B, a polyene antifungal antibiotic produced by a strain of *Streptomyces nodosus*. As described by the Squibb Institute for Medical Research,

amphotericin B "shows a high order of activity against many species of fungi in vitro, but no antibacterial activity." It was felt, however, that the combination of tetracycline and amphotericin B may have produced a synergistic effect.

Accordingly, a series of 196 patients were treated with an identical product, tetracycline phosphate complex, without the amphotericin B. The dosage employed was the same, 500 mg. every 4 hours to a total of 3 grams. As shown in figure 4, at 14 days following treatment the failure rates for the two tetracycline preparations (with and without amphotericin B) were practically identical, 3.4 and 3.6 percent.

Eight additional patients were treated with amphotericin B only, 400 mg. every 4 hours to a total of 2.4 grams. This was four times the dosage of amphotericin B received by the patients treated with tetracycline and amphotericin B combined. One of the eight patients was lost from observation, six were "treatment failures," but the eighth patient, who denied additional treatment, was apparently cured.

Figure 5. Results of test of significance (at 5 percent level) between retreatment rates of various schedules of antibiotic therapy for gonorrhea in males

	Drug	Dosage	Total Amount	Total Cases Treated	Percent Re-treated		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
ORAL	Potassium Phenethicillin	600,000 u. q 12 hours	1,200,000 units	57	28.1	A					E	F	G	H	I	J	K	L	M	N	O	P	Q	R
	Potassium Penicillin G	400,000 u. q 6 hours	2,400,000 units	50	18.0	B									I	J	K		M	N			Q	R
		600,000 u. q 6 hours	1,800,000 units	107	16.8	C				C					I	J	K		M	N			Q	R
	Erythomycin	Single Session	2 grams	136	29.4	D			C		E	F	G	H	I	J	K	L	M	N	O	P	Q	R
		250 mg. q 4 hours	3 grams	184	14.7	E	E			E					I	J	K		M	N			Q	R
		500 mg. q 4 hours	3 grams	61	11.5	F	F			F					I	J								
	Triacetyl-oleandomycin	Single session	2 grams	108	11.1	G	G			G					I	J	K							
		500 mg. q 4 hours	3 grams	193	10.4	H	H			H					I	J	K							
	Tetracycline, Phosphate Potentiated	500 mg. q 4 hours	3 grams	196	3.6	I	I	I	I	I	I	I	I	I				I	I		I	I	I	
	Tetracycline, Phosphate Potentiated With Amphotericin B	500 mg. q 4 hours	3 grams	435	3.4	J	J	J	J	J	J	J	J	J				J	J	J	J	J	J	J
		Single Session	1.5 grams	505	5.7	K	K	K	K	K	K		K	K				K			K	K		
INTRAMUSCULAR	Procaine Penicillin G In Oil	Single Session	1,200,000 units	358	11.2	L	L			L					I	J	K							R
	Aqueous Procaine Penicillin G	Single Session	1,200,000 units	407	8.4	M	M	M	M	M	M				I	J								
	Benzathine Penicillin G	Single Session	1,200,000 units	200	7.0	N	N	N	N	N	N					J								
	Tetracycline Phosphate	Single Session	500 mg.	178	10.7	O	O			O					I	J	K							
	Streptomycin	Single Session	1 gram	411	12.2	P	P			P					I	J	K							R
		Single Session	2 grams	252	8.3	Q	Q	Q	Q	Q	Q				I	J								
	Chloramphenicol	Single Session	1 gram	397	6.5	R	R	R	R	R	R					J		R				R		

Note: Lack of an entry in the square at the intersection of a column and a line means there is no significant difference (at the 5-percent level) between the two schedules involved. When a letter is recorded in the intersection, it means that of the two schedules compared, the schedule indicated by that letter has a significantly lower re-treatment rate.

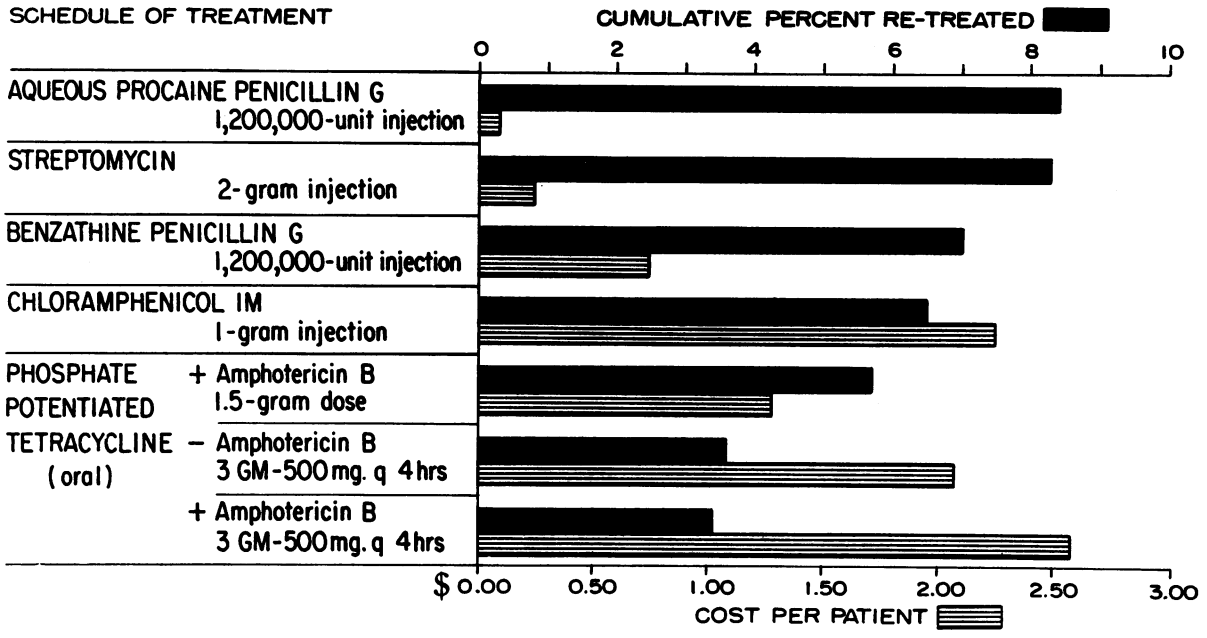
The excellent results obtained with the 3-gram tetracycline schedule were confirmed by the Detroit City Health Department, where the failure rate was 2.6 percent among 196 patients treated with tetracycline and amphotericin B and by the Houston City Health Department, where tetracycline with amphotericin B or tetracycline phosphate, alternated by patients, gave failure rates of 3.3 and 5.7 percent respectively.

Since ideal treatment schedules for venereal disease clinic patients are those which can be administered in a single injection or dose, the next tetracycline schedule evaluated was 1.5 grams in a single dose. The failure rate at 14 days following this treatment schedule was 5.7 percent. As presented in figure 5, the difference in failure rates between the 1.5-gram and 3-gram schedules is no greater than could be attributed to chance. With this exception, the 3-gram schedule (labeled J) was significantly more effective in the treatment of male gonorrhea than any other schedule evaluated.

In selecting a schedule of treatment for routine clinic use, in addition to efficacy of a drug, consideration must be given to factors such as toxicity, ease of administration, change in susceptibility of the gonococcus with continued use, and cost. Among the 18 schedules evaluated there were 7 with failure rates of less than 10 percent. These 7 "best" schedules are ranked in figure 6 by result, and the cost per patient (based on current Government price schedules) is shown for each. The failure rates range from 8.4 to 3.4 percent; the cost of the schedules per patient vary from approximately 9 cents to $2.57. Few antibiotics can compete in price with aqueous procaine penicillin G. The 2-gram streptomycin schedule, which is more expensive than 1,200,000 units of aqueous procaine penicillin G but less expensive than 1,200,000 units of benzathine penicillin G, would appear to be the best substitute for penicillin therapy. Its widespread use, however, is reported to result in resistant strains of the gonococci (*1*, *2*). The excellent results obtained in this evaluation are attributed to the fact that streptomycin has not been used for gonorrhea to any great extent in the Atlanta area.

The cost of phosphate potentiated tetracycline would appear to prohibit its use for routine clinic therapy. It has been demonstrated, however, that the addition of amphotericin B, while increasing its cost, contributes nothing to its effectiveness. Without amphotericin B, a 1.5-gram schedule would cost about

Figure 6. Seven most effective antibiotic schedules in treatment of gonorrhea in males, by retreatment rate and cost per patient



$1.04 per patient. This compares with 74 cents for 1,200,000 units of benzathine penicillin G, the drug now used routinely in many venereal disease clinics. This oral single-dose schedule of tetracycline has obvious advantages—ease of administration, resultant saving in clinic personnel time, and no wastage of the drug. Its greatest assets, however, are that no change in the sensitivity of the gonococcus to tetracycline has been observed (*1*), and that it can be administered with safety. Although patients were questioned carefully about side effects, not a single complaint was registered by the 1,136 patients treated with this drug.

It may be concluded that oral phosphate potentiated tetracycline is a superior drug for the treatment of gonorrhea in the male, and that it provides a safe alternative treatment, even more effective than penicillin, for use by physicians reluctant to use penicillin, for patients sensitive to penicillin, and in instances or areas where low susceptibility of the gonococci to penicillin is suspected.

Summary

From March 1960 through August 1961 more than 4,400 male patients with acute gonorrheal urethritis were treated at the Fulton County Health Department, Atlanta, Ga., on 18 research schedules using 11 different antibiotic preparations. During a 2-week post-treatment observation period, treatment failures by schedule ranged from 3.4 to 29.4 percent.

The most effective drug evaluated was oral phosphate potentiated tetracycline. In a 3-gram dosage (500 mg. every 4 hours) the failure rates were 3.4 and 3.6 percent respectively with and without the addition of amphotericin B to the preparation. In a single 1.5-gram dose the failure rate was 5.7 percent. No complaints of side effects were registered by 1,136 patients treated with this drug. Although phosphate potentiated tetracycline proved superior to the other drugs studied, its cost at present may limit its use.

The most effective intramuscular preparations administered in a single injection included chloramphenicol (1 gram), benzathine penicillin G (1,200,000 units), streptomycin (2 grams), and aqueous procaine penicillin G (1,200,000 units), with failure rates of 6.5, 7.0, 8.3, and 8.4 percent respectively.

NOTE: *Drugs for this study were supplied through the courtesy of E. R. Squibb and Sons, Wyeth Laboratories, Eli Lilly and Company, Parke-Davis Company, and the Upjohn Company.*

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Health Services for State Employees

The history of 10 years of comprehensive health services for State employees in Connecticut, including preemployment examinations, emergency treatment, health counseling and education, immunizations, X-rays, treatment of occupational injuries and diseases, and treatment of nonoccupational illness at the request of a private physician, is reported in the January 1962 issue of *Connecticut Health Bulletin.*

Among other States surveyed, Georgia, Indiana, Kansas, Kentucky, Minnesota, New Hampshire, New Jersey, Oregon, and Pennsylvania reported some health services for State employees. Rhode Island and New York are contemplating establishing such services.