Epidemiologic Treatment of Contacts to Infectious Syphilis

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IN THE CONTROL of syphilis the importance of prompt examination of all contacts of patients with infectious syphilis is universally recognized. After examination immediate epidemiologic treatment of clinically negative recent contacts is an essential part of any adequate control effort.

Knowledge that treatment will be given to any contact exposed to early syphilis within the past 3 months does not relieve the examining clinician of the responsibility for taking a careful history and performing a thorough physical examination. It does not speak well for the examining physician if hidden mucocutaneous lesions, histories of past lesions suggestive of early syphilis, or recent, possibly suppressive antibiotic therapy are brought to light on a second clinic visit after a reactive serologic test has been reported.

The present worldwide resurgence of syphilis has caused new interest in epidemiologic or prophylactic treatment of this disease. Expense of medication, mode and frequency of administration, and side effects all present problems in the large as well as the small control program. The need for determining adequate minimal prophylactic treatment schedules for penicillin and alternate antibiotics is apparent. In addition, there is the problem of seronegative gonorrhea patients without lesions who may be incubating syphilis at the time they receive treatment. Will widely used treatment schedules for uncomplicated gonococcal urethritis in the male eliminate concomitant, incubating syphilis?

These problems prompted the introduction early in 1961 of a cooperative clinical study by the Venereal Disease Branch of the Communicable Disease Center. Venereal disease clinics in Los Angeles, Chicago, Philadelphia, Miami, and Houston are participating.

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Method of Study

The cooperating clinics were requested to use four schedules of treatment and a placebo consecutively on all named sex contacts of infectious syphilis patients. Those included in the studies were residents of the area who were clinically negative for syphilis on initial examination and known to have been exposed within the preceding 3 months. If a serologic test at the time of the initial examination produced a positive reaction, the patient was to be dropped from the study even if there was possibility of a biologic false positive reaction. All others were to be followed for a period of 3 months, with physical inspection for early lesions every 2 weeks and serologic tests for syphilis monthly.

The five schedules included two of benzathine penicillin G (2,400,000 units and 600,000 units) and 600,000 units of aqueous procaine penicillin G, each administered in a single treatment; intramuscular tetracycline phosphate, 1 gram total dosage, administered in two 500-mg. injections on consecutive days, and a placebo.

For placebo, the special diluent for the tetracycline phosphate (glycerine acetal plus lidocaine) was administered on the same schedule as the tetracycline.

Results

As of November 1962, 788 contacts meeting the criteria for study had been treated and observed for periods ranging from 2 weeks to more than 3 months. The number treated on each schedule varied from 126 to 204, and observation in the third month or later ranged from 82 to 88 percent.

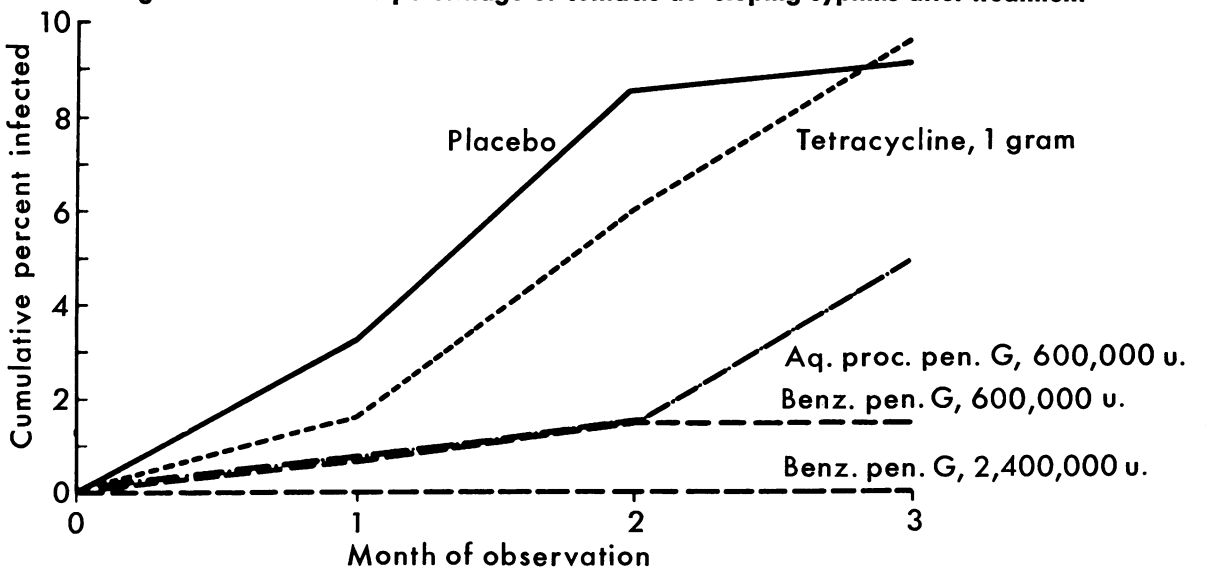
The cumulative percentage of contacts developing syphilis for each schedule of treatment throughout the 3-month observation period is shown in figure 1. The rate of infection following placebo was 9.2 percent. This varied from 15.9 percent if exposure was within 1 month to 2.5 percent if exposure was 2 to 3 months prior to initial examination (see table). One gram of tetracycline phosphate was apparently completely inadequate in aborting incubating syphilis. The 2,400,000-unit benzathine penicillin G schedule is the only antibiotic schedule evaluated in this study which appears to be an effective prophylactic treatment.

Statistically, of course, the difference between the two benzathine penicillin G schedules (none infected following 2,400,000 units compared with 1.5 percent infected following 600,000 units) is not significant. However, the differences between the 2,400,000-unit schedule and the other three are significant at the 1 percent level. Also significant at the 1 percent level are the differences between the benzathine penicillin G schedule of 600,000 units and the tetracycline schedule and the placebo.

Aqueous procaine penicillin G in a dosage of 600,000 units did little more than prolong the incubation period. This observation is even more evident in figure 2, which shows the percentage distribution of subjects developing syphilis by month following treatment. In all but four instances it was possible to determine with a fair degree of accuracy in which month of observation syphilis could have been detected, although infection was not always diagnosed in the primary stage. In the four questionable cases, all of which were treated with tetracycline, distribution by month in which syphilis developed has been made according to the distribution of the known cases.

Although the number of subjects (35) who developed syphilis is small, there appears to be a definite pattern. In the placebo group, 38 percent of the infections developed within the first month of observation and 56 percent during the second month. In contacts treated with tetracycline, the appearance of syphilis was slightly delayed—46 percent of the infections developed in the second month of observation

Figure 1. Cumulative percentage of contacts developing syphilis after treatment



and 36 percent in the third month. In patients treated with aqueous procaine penicillin G, two-thirds of the infections were not evident until the third month (60–90 days) following treatment.

Comment

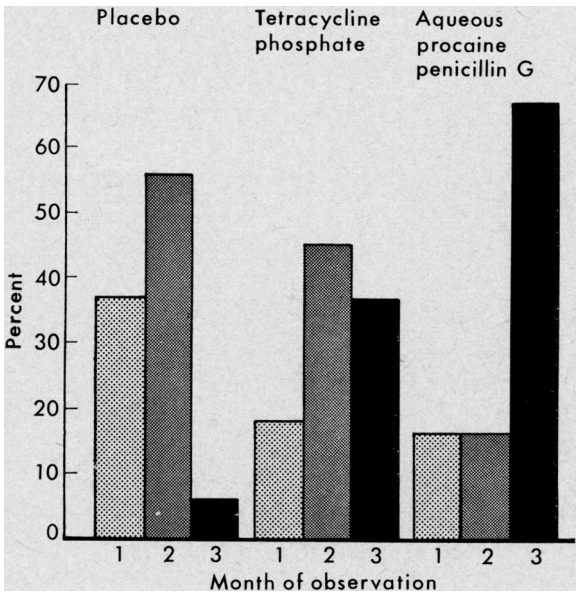
It is possible that the delayed infections following tetracycline and aqueous procaine penicillin might in actuality be infections from reexposure, since neither drug supplies the duration of protection provided by benzathine penicillin G. In considering this possibility it is necessary to explain why only one of the contacts in the placebo group remaining under observation developed syphilis in the third month if all groups had the same opportunity for reexposure. Let us assume that some individuals who might be termed "syphilis susceptible" contract syphilis on exposure while others do not. These syphilis susceptible individuals in the placebo group (with one exception) devel-

Number of contacts on each treatment schedule and cumulative percentage developing syphilis during a 3-month observation period, by time since exposure

Treatment schedules	Time since exposure (months)	Observations for syphilis									
		First month			Second month				Third month			
		Total observed [1]	Developed syphilis		Total observed [1]	Developed syphilis			Total observed [1]	Developed syphilis		
			Number	Percent		Number	Percent	Cumulative percent		Number	Percent	Cumulative percent
1. Benzathine penicillin G 2,400,000 units.	<1	113	0	0	105	0	0	0	96	0	0	0
	1–2	47	0	0	42	0	0	0	39	0	0	0
	2–3	44	0	0	42	0	0	0	41	0	0	0
	Total	204	0	0	189	0	0	0	176	0	0	0
2. Benzathine penicillin G 600,000 units.	<1	70	0	0	68	0	0	0	60	0	0	0
	1–2	34	1	2.9	31	0	0	2.9	29	0	0	2.9
	2–3	33	0	0	31	1	3.2	3.2	25	0	0	3.2
	Total	137	1	.7	130	1	.8	1.5	114	0	0	1.5
3. Aqueous procaine penicillin G 600,000 units.	<1	65	1	1.5	61	1	1.6	3.1	56	3	5.4	8.5
	1–2	41	0	0	39	0	0	0	34	1	2.9	2.9
	2–3	33	0	0	27	0	0	0	24	0	0	0
	Total	139	1	.7	127	1	.8	1.5	114	4	3.5	5.0
4. Tetracycline	<1	59	2	3.4	54	4	7.4	10.8	53	3	5.7	16.5
	1–2	36	0	0	32	1	3.1	3.1	31	0	0	3.1
	2–3	31	0	0	27	0	0	0	26	1	3.8	3.8
	Total	126	2	1.6	113	5	4.4	6.0	111	4	3.6	9.6
5. Placebo	<1	79	3	3.8	75	8	10.7	14.5	70	1	1.4	15.9
	1–2	63	2	3.2	61	1	1.6	4.8	58	0	0	4.8
	2–3	40	1	2.5	35	0	0	2.5	30	0	0	2.5
	Total	182	6	3.3	171	9	5.3	8.6	158	1	.6	9.2
All schedules	<1	386	6	1.6	363	13	3.6	5.2	334	7	2.1	7.3
	1–2	221	3	1.4	205	2	1.0	2.4	191	1	.5	2.9
	2–3	181	1	.6	162	1	.6	1.2	146	1	.7	1.9
	Total	788	10	1.3	729	16	2.2	3.5	671	9	1.3	4.8

[1] Adjusted for cases lost from observation in accordance with method described in reference 3.

Figure 2. Percentage distribution of infected contacts, by month syphilis developed after treatment



oped syphilis during the first 2 months of observation, were treated, and were removed from the group at risk to infection in the third month. If syphilis were aborted in the syphilis susceptible individuals treated with tetracycline or aqueous procaine penicillin, these same individuals would have been at risk to reinfection during the entire 3-month observation period.

Early animal studies by Eagle, Magnuson, and Fleischman (*1*) suggested a direct relationship between the period of time following infection and the amount of penicillin required to cure the disease. Cutler, Olansky, and Price (*2*) in 1955 reported good results in the treatment of seronegative, darkfield positive primary syphilis with 300,000 units of procaine penicillin G in oil with aluminum monostearate (PAM). Because of this information, it has been widely felt that 600,000 units of penicillin G given intramuscularly in the treatment of gonorrhea would be ample to cure seronegative incubating syphilis acquired at the same time or prior to the gonorrhea being treated. The results with the two intramuscular penicillin preparations at the 600,000-unit level are therefore unexpected and alarming. The disappointing results of the two-dose intramuscular tetracycline schedule also are unfortunate but are easier to explain than the penicillin failures.

Of 788 contacts followed, 35, or 4.8 percent, developed syphilis. If the percentage of contacts developing syphilis in the placebo group (9.2) applied to the whole study group, 72 persons would have developed syphilis. All cases could have been prevented with 2,400,000 units of benzathine penicillin G.

Because of the failures demonstrated with the two penicillin preparations at the 600,000-unit level and the intramuscular tetracycline, the study is being continued with the following substitutions of drugs and schedules:

1. Benzathine penicillin G—1,200,000 units in a single injection.
2. Procaine penicillin G in oil with aluminum monostearate—1,200,000 units in a single injection.
3. Chloramphenicol intramuscular—1 gram.
4. Chloramphenicol intramuscular—2 grams (single 1-gram injection on 2 consecutive days).
5. Placebo.

Benzathine penicillin G in a 1,200,000-unit dosage was selected in the hope that it would be equally as effective as the 2,400,000-unit schedule in aborting incubating syphilis. Procaine penicillin G in oil (PAM) in a 1,200,000-unit dosage is the most commonly used schedule for the treatment of gonorrhea in venereal disease clinics. Chloramphenicol IM (which is effective in the treatment of early syphilis and which has never produced a reported serious reaction when used for that purpose) was chosen as a possible alternate antibiotic for penicillin sensitive patients.

Summary

In a cooperative clinical study, several intramuscular treatment schedules were tested for their effectiveness in preventing the development of syphilis in persons who had been exposed to infectious syphilis. The study population consisted of 788 clinically and serologically negative contacts at five treatment centers. A part of the study group received a placebo similar in appearance to one of the drugs being tested and given in the same manner.

No cases developed among contacts treated with 2,400,000 units of benzathine penicillin G given in one treatment at one or two intramuscular injection sites. Intramuscular injections of 600,000 units of aqueous procaine penicillin G or of benzathine penicillin G or an intramus-

cular tetracycline preparation given in a dosage of 500 mg. on 2 successive days gave unsatisfactory results. Of 182 patients given placebo, 16, or 9.2 percent (cumulative rate based on number observed for varying periods) developed syphilis during the 3-month followup period.

REFERENCES

(1) Eagle, H., Magnuson, H. J., and Fleischman, R.: Relation of the size of the inoculum and the age of the infection to the curative dose of penicillin in experimental syphilis, with particular reference to the feasibility of its prophylactic use. J Exp Med 85: 423–440 (1947).

(2) Cutler, J. C., Olansky, S., and Price, E. V.: Treatment of early syphilis: results with penicillin G procaine and two percent aluminum monostearate. AMA Arch Derm 71: 239–244 (1955).

(3) Iskrant, A. P., Bowman, R. W., and Donohue, J. F.: Techniques in evaluation of rapid antisyphilitic therapy. Public Health Rep 63: 965–977 (1948).

NOTE: Tetracycline phosphate and the special diluent used as the placebo in this study were supplied by the Upjohn Company.

Education Notes

Ergonomics and Cybernetics for Nurses. The Loughborough College of Technology, Loughborough, England, conducts a 1-year, full-time, postgraduate course for occupational health nurses on ergonomics and cybernetics. The wide scope of the syllabus offers nurses an opportunity to study with engineers, architects, designers, and students in the social, biological, and physical sciences. Practical work takes up half of the time. In ergonomics, the nurses study the capabilities and limitations of human performance at work, with the objective of improving the effectiveness and well-being of the individual through design and control; in cybernetics, the science of systems, they study processes of control and information flow. Tuition fees for the current term, which began on October 1, 1963, are £75 and accommodations 6 guineas per week for full board and residence in the college hall. Further details may be obtained from: Head of the Department of Ergonomics and Cybernetics, Loughborough College of Technology, Loughborough, Leicestershire, England.

Master's Degree in Radiological Health. The Department of Sanitary Science and Public Health of the University of Oklahoma offers a 12-month program in radiological health leading to a master's degree. The new program, supported by the Public Health Service, is open to chemists, physicists, and biologists, as well as engineers. It allows maximum utilization of the candidates' previous training and experience. Stipends are offered at $3,600 a year, with fee and tuition reduction. Professor George Reid, Coordinator, Department of Sanitary Science and Public Health, University of Oklahoma, Norman, Okla., will supply additional information.