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STUDIES IN THE HOME TREATMENT OF STREPTOCOCCAL DISEASE*

II. A Comparison of the Efficacy of Oral Administration of Penicillin and Intramuscular Injection of Benzathine Penicillin in the Treatment of Streptococcal Pharyngitis

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PATIENTS with streptococcal pharyngitis were formerly treated by the Home Medical Service of the Massachusetts Memorial Hospitals with a seven-day course of penicillin by mouth. However, when it became apparent that more than a third of these patients were failing to take the full prescribed course of penicillin, it was decided to change to intramuscular injections of benzathine penicillin.[1]

There have been many favorable reports in the recent literature concerning the effectiveness of a single injection of benzathine penicillin G for the treatment of infections with the beta-hemolytic streptococcus.[2-4] A single injection of 600,000 units of this repository penicillin has been reported to maintain penicillin blood levels for a period of twelve to fourteen days in the majority of patients.[2,5,6] This agent, therefore, seems to have a distinct advantage in the treatment of such infections in that it would allow the physician to institute adequate therapy on first seeing the patient without having to rely on the patient's faithfulness in taking oral medication. It would also obviate the necessity of giving two or three additional injections as with procaine penicillin.

Before the change to this long-acting penicillin was made, it was decided to compare a group of patients having streptococcal pharyngitis treated with penicillin by mouth with a similar group treated with injections of benzathine penicillin.

METHODS

Only patients with clinical evidence of pharyngitis and positive throat cultures for beta-hemolytic streptococci were included in this study.

During the period November, 1954, through January, 1955, all patients were treated with 200,000 units of buffered potassium penicillin G by mouth three times daily for seven days (total of 4,200,000 units).

During the period February, 1955, through April, 1955, all patients were treated with a single injection of benzathine penicillin.‖ Children fifteen years of age or younger received 600,000 units, whereas all patients over fifteen received 900,000 units.

There were 127 patients in the group treated with penicillin by mouth and 196 patients in the group treated with benzathine penicillin by injection. Of the total 323 patients, 276 (85.4 per cent) were fifteen years of age or younger, and 47 (14.6 per cent) were older than fifteen.

In the group treated orally one follow-up throat culture was obtained between the fourth and seventh days of therapy, and another on the tenth day (that is, three days after the discontinuance of therapy). The tenth day was chosen because it was believed that the reappearance of beta-hemolytic streptococci in cultures would more probably be due to relapse than to reinfection.

In the group receiving benzathine penicillin the first follow-up culture was obtained between the fourth and the eighth day after injection, and subsequent cultures on the fourteenth, seventeenth and

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‖Kindly supplied as Bicillin by Wyeth Laboratories, Philadelphia.

twenty-first days. Since most patients have significant blood levels for fourteen days,[2,5,6] it was hoped that the seventeenth day of the benzathine-penicillin regimen would correspond to the tenth day of the oral regimen.

Treatment was begun and the initial follow-up culture was obtained by supervised Boston University medical students who spend one month during their senior year on the Home Medical Service. All additional follow-up cultures were obtained by one of us (D. N. M. or D. G. W.).

TABLE 1. *Positive Follow-up Throat Cultures in Patients Treated with Penicillin by Mouth (600,000 Units Daily for Seven Days).*

PATIENT PERFORMANCE	NO. OF PATIENTS	PATIENTS WITH POSITIVE FOLLOW-UP CULTURES
Penicillin as prescribed	90	10(11.1%)
Less penicillin than prescribed	37	12(32.4%)
Totals	127	22(17.3%)

All throat cultures were obtained by direct vision with sterile cotton swabs, planted within one or two hours on blood-agar plates containing 5 per cent horse blood, and read within eighteen to twenty-four hours.

When follow-up cultures were obtained, the patients were carefully observed for any evidence of penicillin reaction, recurrence of streptococcal infection, or streptococcal complications. Patients receiving penicillin by mouth were questioned regarding the amount of penicillin taken. Those treated with benzathine penicillin were questioned concerning discomfort at the site of injection.

TABLE 2. *Positive Follow-up Cultures in Relation to the Number of Days Penicillin Was Taken by Mouth.*

NO. OF DAYS PENICILLIN TAKEN	NO. OF PATIENTS	PATIENTS WITH POSITIVE FOLLOW-UP CULTURES
7	90	10(11.1%)
5-7	17	4(23.5%)
<5	20	8(40.0%)
<4	8	6(75.0%)

RESULTS

Group Receiving Penicillin by Mouth

Of the 127 patients in this group (Table 1) 22, or 17.3 per cent, had positive follow-up cultures for beta-hemolytic streptococci. Among the 90 patients who stated that they took the prescribed course of penicillin, there were 10, or 11.1 per cent, positive follow-up cultures, whereas among the 37 patients who admitted to taking less than the prescribed amount, there were 12, or 32.4 per cent, whose follow-up cultures were positive, a statistically significant difference ($P < 0.01$).*

The percentage of positive follow-up cultures varied inversely with the number of days the patient took the medication (Table 2).

Only 1 positive follow-up culture occurred between the fourth and seventh days in the group taking the prescribed amount of penicillin, whereas 6 positive follow-up cultures occurred during this time among the 37 patients taking the drug improperly. On the tenth day 10 positive follow-up cultures occurred among 90 patients taking the penicillin as prescribed, and 11 among 37 patients taking less than the prescribed amount. Results of follow-up cultures in relation to the day obtained are shown in Table 3.

TABLE 3. *Positive Follow-up Throat Cultures in Relation to the Day Culture Was Obtained.*

DAY CULTURE OBTAINED*	NO. OF PATIENTS	PATIENTS WITH POSITIVE CULTURES
All patients:		
1	127	127(100.0%)
4-7	127	7(5.5%)
10	125†	21(16.8%)
Patients taking penicillin as prescribed:		
1	90	90(100.0%)
4-7	90	1(1.1%)
10	90	10(11.1%)

*Penicillin started on day 1.
†Two patients could not be found for 10th-day follow-up culture.

It is of interest that no clinical relapse of pharyngitis was noted in any of this group of patients followed for ten days. However, 1 patient who took the penicillin for only one day did not recover from his pharyngitis and was given penicillin intramuscularly. It is possible that some of these patients suffered clinical relapses several days after the final follow-up study, but it is believed that most of them would have called the Home Medical Service again if this had occurred. Table 4 gives a summary of the data obtained in patients who had bacteriologic recurrences.

Group Receiving Benzathine Penicillin by Injection

There were 196 cases treated with benzathine penicillin. Four patients were included in the study twice during this three-month period, intervals of twelve, nine, four and three weeks elapsing between the two infections. The last patient was the only one treated with benzathine penicillin who suffered what may have been a clinical relapse during the three-week follow-up period. This three-year-old girl had a temperature of 102°F. twenty days after

*Values for P were obtained by the chi-square method using a four-fold contingency table.

injection; beta-hemolytic streptococci were found again on throat culture.

Among the 195 patients on whom follow-up throat cultures were obtained, 11 (5.6 per cent) had positive cultures. There were 1.6 per cent positive cultures four to eight days after treatment, 0.6 per cent after fourteen days, 3.2 per cent after seventeen days, and 4.4 per cent after twenty-one days (Table 5). The discrepancy in the total number of cultures obtained on any given day and the total number of patients in the study is due to 9 patients who could not be followed for the complete period of three weeks for various reasons* and the occasional situation in which the patient could not be reached for 1 or more of the follow-up cultures.

TABLE 4. *Summary of Data on Patients Treated with Penicillin by Mouth Who Had Bacteriologic Recurrences.*

PATIENT	AGE	NO. OF DAYS PENICILLIN TAKEN	DAY OF FOLLOW-UP CULTURE		REMARKS*
	yr.				
R.W.	3	7	7,	10†	Otitis media & measles
D.H.	4	1	7,†	9†	Persistent pharyngitis & fever
B.S.	46	7	7,	10†	
J.H.	6	7	7,	10†	
M.R.	10	6⅔	7,	10†	
C.C.	3	3⅓	7,†	10†	Scarlet fever
K.C.	4	3⅓	7,	10†	Scarlet fever
R.B.	22	2⅔	7,†	10†	
A.M.	7	7	7,	10†	
E.E.	5	7	7,	10†	
R.R.	8	7	7,	10†	
P.G.	5	7	7,	10†	
R.M.	3	3	7,†	10†	
D.S.	3	1⅓	7,	10†	
R.H.	9	7	7,†	10†	
P.G.	3	6	7,†	10†	
C.P.	6	6	7,	10†	Otitis media
W.B.	6	4	7,	10†	
D.B.	4	7	7,	10†	Scarlet fever
E.A.	4	4	7,	10†	
R.T.	3	7	7,	10†	
C.R.	25	3⅓	7,†	10	

*Diagnoses in addition to pharyngitis listed here, as well as any clinical relapse, complication or failure to respond.
†Culture positive for beta-hemolytic streptococci.

*Two patients had negative cultures on the fifth and seventh days after treatment and were then admitted to the hospital for tonsillectomy. Two patients had negative cultures five days after treatment and were subsequently admitted to the hospital because of symptoms suggestive of acute rheumatic fever (both are described in detail below in the section on penicillin reactions). Two patients had negative cultures three days and seven days after treatment and then moved out of the area covered by the Home Medical Service. One patient with a negative culture on the seventh day had a temperature elevation to 104°F. on the following day; she was taken to an outpatient department and received additional penicillin intramuscularly. One patient had a negative culture six days after treatment and refused further cultures. One patient called a private doctor because of persistence of fever and sore throat on the day after treatment.

No patient failed to have a clinical response to benzathine penicillin within forty-eight hours, and the majority responded within twenty-four hours. Two patients had moderate injection of the pharynx accompanying bacteriologic recurrence; 1 of these also had antral sinusitis.

There were 2 patients who had positive cultures on the fourth and sixth days respectively after treatment, the remaining 3 follow-up cultures being negative. Both had only a rare colony of beta-hemolytic streptococci on the cultures. This accounts for the fact that there were 3 patients with positive follow-up cultures four to eight days after treatment and only 1 with a positive culture at the end of two weeks. A summary of the data concerning the patients with bacteriologic recurrences is presented in Table 6.

TABLE 5. *Positive Follow-up Throat Cultures in Patients Treated with Benzathine Penicillin in Relation to the Day Culture Was Obtained.*

DAY CULTURE WAS OBTAINED*	NO. OF CULTURES	PATIENTS WITH POSITIVE CULTURES
1	196	196(100.0%)
4-8	186	3(1.6%)
14	182	1(0.6%)
17	185	6(3.2%)
21	183	8(4.4%)
Total patients with follow-up cultures	195†	11(5.6%)

*Benzathine penicillin administered on day 1.
†One patient had no follow-up cultures.

TABLE 6. *Summary of Data on Patients Treated with Benzathine Penicillin Who Had Bacteriologic Recurrences.*

PATIENT	AGE	DOSAGE OF BENZATHINE PENICILLIN	DAY OF FOLLOW-UP CULTURE				REMARKS*
	yr.	*units*					
V.C.	11	600,000	—,	13,	16,†	20	Otitis media
F.F.	12	600,000	7,†	14,†	17,	21†	
C.F.	7	600,000	8,	15,	17,†	21†	Moderate injection of pharynx
J.M.	15	600,000	6,	—,	18,	21†	
C.D.	8	600,000	6,†	14,	17,	21	
J.G.	30	900,000	4,	15,	17,†	21†	Sinusitis & moderate injection of pharynx
F.J.	20	900,000	4,	15,	17,†	21†	
J.M.	2	600,000	7,	14,	17,†	21†	
S.K.	6	600,000	7,	14,	17,	20†	Temperature of 102°F. on 20th day
A.A.	8	600,000	4,†	14,	17,	21	
K.B.	9	600,000	5,	14,	17,†	21†	

*Diagnoses in addition to pharyngitis listed here, as well as any clinical relapse, complication or failure to respond.
†Culture positive for beta-hemolytic streptococci.

Comparison of Two Groups

The comparability of the patients is indicated by the age, sex, race, presence of tonsils, and initial throat-culture results in the two groups (Table 7). It was not possible to select the patients at random for this study so that a significant bias exists in that oral treatment with penicillin was studied during the months of November, December and January, whereas treatment with benzathine penicillin was studied during the months of February, March and April. The prevalence of streptococcal disease was higher during the latter three months, as indicated by the number of patients suitable for study during each period. There was a higher percentage of nonwhite patients and patients with tonsils in the group treated orally, but there was no evidence in this study that either of these factors played a significant part in influencing the culture results.

TABLE 7. *Comparable Data in the Two Groups.*

DATUM	PATIENTS RECEIVING PENICILLIN BY MOUTH		PATIENTS RECEIVING BENZATHINE PENICILLIN	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Patients <15 yr. of age	110	86.6	166	84.6
Female patients	67	53.8	100	51.0
Nonwhite patients	67	53.8	75	38.2
Patients with tonsils	113	91.1	163	84.0
Patients with initially positive throat culture	127	100.0	196	100.0
Months of treatment	November-January		February-April	
Total patients in study	127		196	

TABLE 8. *Comparison of Results of Follow-up Culture between Patients Receiving Penicillin by Mouth and Benzathine Penicillin.*

GROUP	NO. OF PATIENTS	NO. OF PATIENTS WITH POSITIVE FOLLOW-UP CULTURES	PERCENTAGE
Treatment with penicillin by mouth	127	22	17.3
Treatment with benzathine penicillin	195	11	5.6

The efficacy of treatment with the two methods is compared in Table 8, which shows that 17.3 per cent of the patients receiving penicillin by mouth and only 5.6 per cent of those treated with benzathine penicillin by injection had positive follow-up cultures, a highly significant difference ($P<0.001$). This difference is even more striking when it is considered that in the former group only 2 follow-up cultures were obtained over a ten-day period, whereas in the latter 4 follow-up cultures were obtained over a twenty-one-day period.

When cultures obtained on the tenth day in the group receiving oral treatment are compared with those obtained on the seventeenth day in the group in which benzathine penicillin was given by injection (assuming each to be approximately three days after disappearance of significant levels of penicillin from the blood), there were 16.8 per cent positive cultures among the former and only 3.2 per cent positive cultures among the latter, again a highly significant difference ($P<0.001$). If only patients taking the prescribed amount of penicillin by mouth are included, there were 11.1 per cent positive cultures in this group — a difference still considered significant ($P<0.02$).

In the evaluation of the over-all effectiveness of the two types of therapy, it is more realistic to include all patients in the group treated by mouth, regardless of whether or not they received the full course of penicillin, since this may give a better total picture of therapy by this method.

Household Contacts

During the six-month period of this study, throat cultures were obtained on 450 available household contacts. One hundred and twenty-five, or 27.8 per cent, of these were positive for beta-hemolytic streptococci. All contacts who had positive cultures were treated with therapeutic doses of penicillin. Of the 125 contacts with positive cultures, 46, or 38.4 per cent, had symptoms and were classified as secondary cases.

It is interesting that of the 322 contacts fifteen years of age or younger, 112 (34.8 per cent) had positive cultures; of the 128 contacts older than fifteen, only 13, or 10.8 per cent, had positive cultures, a statistically significant difference ($P<0.01$).

Reactions

There were no observed systemic reactions in any of the 127 patients treated with penicillin by mouth.

One hundred and eighty of the patients treated with benzathine penicillin were questioned and observed concerning local discomfort at the site of injection. One hundred and twenty-five, or 69.4 per cent, of these patients stated that they had discomfort. This lasted from one to seven days, with an average of two and six-tenths days.

The discomfort consisted of pain and persistent tenderness at the site of injection that was severe enough in some children to cause limping. However, only 4 patients stated that the pain was severe enough to keep them awake at night or require analgesics. No abscess formation or objective signs of inflammation were observed. Several patients had small, nontender nodules at the site of injection that persisted for as long as three weeks.

Among all the patients treated with benzathine penicillin (196 in the culture study followed for three weeks and 302 additional patients* followed for at

*These asymptomatic contacts and patients treated for pharyngitis from whose throats beta-hemolytic streptococci were not isolated were followed for at least one week. They were observed for reactions but were not recultured.

least one week), 510 injections were given to 498 patients. Four hundred and thirty-seven of these injections contained 600,000 units given to patients fifteen years of age or younger, and 73 contained 900,000 units given to patients older than fifteen. There were only 5 patients of this entire group who were observed to have signs and symptoms suggesting the possibility of a systemic reaction to penicillin. Four of these had no rash at the time of injection, and nonspecific rashes subsequently developed several hours to eight days after injection. Another patient had a rash at the time of injection, and a different type of rash developed subsequently. The pertinent details concerning these patients are as follows:

CASE 1. S. F., a 2-year-old girl, was treated with 600,000 units of benzathine penicillin for acute streptococcal pharyngitis. Approximately 6 hours after injection, a scarlatiniform eruption developed, lasting for 2 days. She had received penicillin previously.

CASE 2. D. P., a 3-month-old girl, received 600,000 units of benzathine penicillin for acute pharyngitis. She manifested a fine papular nonpruritic eruption 4 hours after injection that lasted for 3 days. She had received penicillin previously.

CASE 3. D. S., a 3-year-old Negro girl, received an injection of 600,000 units of benzathine penicillin for acute streptococcal pharyngitis. A fine papulovesicular pruritic eruption occurred 24 hours later and lasted for 3 days. There was no history of previous penicillin administration.

CASE 4. S. M., an 8-year-old girl, had fever, a generalized morbilliform eruption, erythema multiforme and generalized arthralgia when first seen. Because of injection of the pharynx and the presence of beta-hemolytic streptococci on throat culture, she was given an injection of 600,000 units of benzathine penicillin. The morbilliform eruption subsided in 2 days, but the erythema multiforme persisted. Nine days after the injection, a third type of rash, a generalized papulovesicular pruritic eruption, developed. At that time, the white-cell count was 19,000, and the sedimentation rate was 35 mm. per hour. The symptoms strongly suggested acute rheumatic fever, and she was admitted to the Boston City Hospital. In the hospital the fever, leukocytosis and elevated sedimentation rate persisted for several days, but there was no objective evidence of carditis or arthritis. She was also found to have pediculosis. The erythema multiforme subsided several days after admission; the papulovesicular eruption became hemorrhagic and persisted for 2 weeks. It was believed that she did not have rheumatic fever and that the continuing eruption probably represented a "toxic dermatitis," penicillin and pediculosis being possible etiologic agents.

CASE 5. J. P., a 13-year-old Negro, called because of a painful left knee with a history of having had pain in both knees intermittently for 4 years. He was also noted to have a mild pharyngitis, and throat culture was positive for beta-hemolytic streptococci. He was therefore treated with an injection of 600,000 units of benzathine penicillin. Eight days after injection erythema marginatum and a papulovesicular pruritic eruption developed. Because of the former rash, painful swelling of the left knee, a Grade 2 apical systolic murmur (this murmur had also been noted 4 years previously), a temperature of 99.5°F., a white-cell count of 11,000 and a sedimentation rate of 56 mm. in 1 hour, he was admitted to the Massachusetts Memorial Hospitals with a suspicion of acute rheumatic fever. In the hospital, the swelling of the left knee and the erythema marginatum subsided in 2 days. The papulovesicular eruption lasted for 6 days, and antihistamines were required for control of the itching. There was no evidence of carditis, and the diagnosis of rheumatic fever remained in doubt. An L. E.-cell preparation was negative, as were 2 skin tests for penicillin sensitivity. He had received penicillin previously. It was believed that he probably had had a penicillin reaction.

Eliminating Case 1, who probably had scarlet fever and not a penicillin reaction, there were 4 patients who possibly had penicillin reactions, a rate of occurrence of 0.8 per cent out of 510 injections of benzathine penicillin.

It is of interest that no systemic reactions were observed in patients over fifteen years of age who received 900,000 units of benzathine penicillin. However, this was a relatively small group — 73 patients.

Complications

No suppurative complications were observed in either group of patients. There were no definite cases of acute rheumatic fever among patients in the study; 2 patients with possible cases were admitted to the hospital, but the diagnosis was not established. These were Cases 4 and 5, described above. Both patients had symptoms suggestive of rheumatic fever before receiving penicillin. No cases of acute glomerulonephritis were observed.

Summary and Conclusions

It would appear from this study that, for keeping the throat free of beta-hemolytic streptococci, a single injection of benzathine penicillin is more effective (94.4 per cent of patients for twenty-one days) than a seven-day course of penicillin by mouth (82.4 per cent for ten days). Also benzathine penicillin has the advantage of being less expensive than other standard forms of therapy for streptococcal pharyngitis now in use and eliminates the problem of patient reliability in taking oral medication.

It should be borne in mind that this study reveals circumstances that develop in problems of patient management in an uncontrolled environment in which the opportunity for reinfection and relapse is most likely. The results obtained under such adverse, but nevertheless realistic, conditions indicate that effective treatment could be obtained with benzathine penicillin in approximately 95 per cent of patients.

Of 127 patients with acute pharyngitis due to the beta-hemolytic streptococcus treated at home with a seven-day course of penicillin by mouth, 22, or 17.3 per cent, had bacteriologic recurrences during a ten-day follow-up period. Of 196 patients treated at home with a single injection of benzathine penicillin, 11, or 5.6 per cent, had bacteriologic recurrences during a three-week follow-up period.

Of the patients receiving benzathine penicillin, approximately 70 per cent complained of discomfort at the site of injection for an average of two and a half days.

There were 4 possible systemic penicillin reac-

tions observed after 510 injections of benzathine penicillin, a frequency of 0.8 per cent.

It is concluded that a single injection of benzathine penicillin is effective therapy for pharyngitis due to the hemolytic streptococcus, the main advantage over penicillin by mouth being that it assures the patient of receiving the intended therapy. The observations presented here deal with a comparison of intramuscular injection of benzathine penicillin G and should not be interpreted as implying any comparison with the oral route of administration of benzathine penicillin G, which was not used.

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POSTOPERATIVE BILE-DUCT STRICTURES*

Their Etiology and Treatment

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TWENTY years ago it was possible for Eliot[1] to collect all 215 cases of postoperative biliary strictures reported in the literature here and abroad. In a painstaking and brilliant fashion he reviewed each case and made many observations that, if heeded over the intervening years, might have given improved results in the care of this difficult group of patients. In recent years, sizable series of cases have appeared from various clinics, some of them running into hundreds of patients, and it is of some concern whether or not the injury to bile ducts during the course of cholecystectomy has actually become more frequent. Removal of the gall bladder has certainly become a common procedure, performed by many occasional operators, and in point of frequency is second only to appendectomy in the field of abdominal surgery. It may be fair to state that duct stricture after cholecystectomy has not decreased in frequency over the years, in spite of advances in graduate training.

Etiology

Our interest in this problem has included investigation into the etiology of these postoperative strictures. Eighty original operative notes are available from forty-three different hospitals. Eighty-one strictures occurred after operations on the biliary tract, three after subtotal gastrectomy, and one after a porta-cava shunt procedure. Two benign strictures were found in patients who had not undergone surgery of any nature (Table 1). Gallstones were present in 89 per cent of the group subjected to cholecystectomy, and only 22 per cent of these procedures were carried out in the presence of acute inflammatory disease. It is worthy of special note that 80 per cent of the gall bladders in this group of injured or later narrowed hepatic ducts were removed in a retrograde fashion, from the cystic duct to the fundus. Sixteen per cent of the operative notes reported excessive bleeding, and in 4 cases large clamps were left in situ as the operative wound was rapidly closed. In 26 per cent of the group concomitant choledochostomy was performed, and in some of the cases this procedure may have resulted in duct in-

TABLE 1. *Biliary-Tract Strictures in 87 Cases,* 1926-1955.

TYPE OF STRICTURE	NO. OF CASES
Postoperative:	
Cholecystectomy	62
Cholecystectomy & choledochostomy	19
Gastrectomy	3
Porta-cava shunt	1
Nonoperative	2
Total	87

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