

Reevaluation of Reactions to Penicillin in Venereal Disease Clinic Patients

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MORE than a quarter of a million patients are treated with penicillin annually in venereal disease clinics throughout the United States. Although other antibiotics, such as the tetracyclines, erythromycin, and chloramphenicol, are therapeutically effective for both syphilis and gonorrhea, their comparatively higher price and lack of repository forms restrict their use to patients who are sensitive to penicillin. In the absence of an economically feasible and clinically practical substitute for penicillin in the routine treatment of venereal disease, reports of increases in the incidence of severe reactions or deaths attributable to penicillin are viewed with concern by health authorities responsible for the control of venereal disease.

Since penicillin therapy constitutes such a vital part of the control program, the Venereal Disease Branch of the Public Health Service has conducted two studies, one in 1954 (1,2) and the other in 1959 (3,4), to evaluate the incidence and severity of reactions to penicillin among venereal disease patients. The following report of the 1959 study includes a comparative analysis of the data collected in 1954.

Method of Study

Sixty-four health departments in 21 States, the District of Columbia, and Puerto Rico and 5 border reception centers participated in a cooperative study to determine the present inci-

dence of reactions to penicillin among patients treated for venereal disease (see p. 192). The participating clinics were requested to submit a study card for each patient treated with penicillin during a 3-month period. Since this 3-month period did not run concomitantly at all clinics, the actual collection of records extended from March 1959 through March 1960. On the card the reactions were classified into three broad categories—anaphylaxis, serum sickness, and urticaria, with a space provided for other reactions not falling into these three groups. A description of the reaction, which for the majority of patients was supplied as requested on the card, permitted a more uniform classification of reactions and a division of anaphylactoid reactions between "mild" and "moderate to severe."

The following instructions were given to the cooperating clinics:

Participants are requested (1) to detain patients in the clinic, if possible, for approximately 30 minutes following penicillin injection and (2) to instruct patients to report back to the clinic if they have any symptoms or complaints within 2 weeks following treatment. Although no special followup is being requested, if these two measures are followed, all immediate reactions and most severe delayed reactions will come to the attention of the clinician.

A Penicillin Reaction Study Card should be completed for each patient treated with penicillin, regardless of the diagnosis. Cards for patients on single-injection therapy may be mailed to the Venereal Disease Branch on the day of treatment or weekly, depending upon clinic volume. Cards for patients on multiple-injection schedules should be retained in the clinic until the planned schedule has been completed.

A second card should be submitted if a reaction is observed after the first card has been mailed. Complete the entire card and be sure to indicate on the last line that a card has been previously submitted.

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The border reception centers supplied a monthly tabulation, by age and history of previous penicillin therapy, of all Mexican braceros treated during the month, completing a study card only for those experiencing reactions. This same procedure was followed by Dade County, Fla. All other participating clinics conducted the study as outlined.

Comparison of Clinics and Reception Centers

The incidence of reactions reported is shown by type in table 1. During the study period 35,496 patients were treated with penicillin, 25,550 in venereal disease clinics and 9,946 at the border reception centers. Reactions were reported in 255, or in 7.2 per 1,000 patients treated.

In venereal disease clinics the incidence was 9.7 per 1,000 patients treated. Urticaria was the most frequent type of reaction, occurring in 5.7 per 1,000. Anaphylaxis was observed in 27, or 1.1 per 1,000. However, in only 9 was it classified as moderate to severe. Serum sickness was reported in 11.

At the border reception centers the incidence

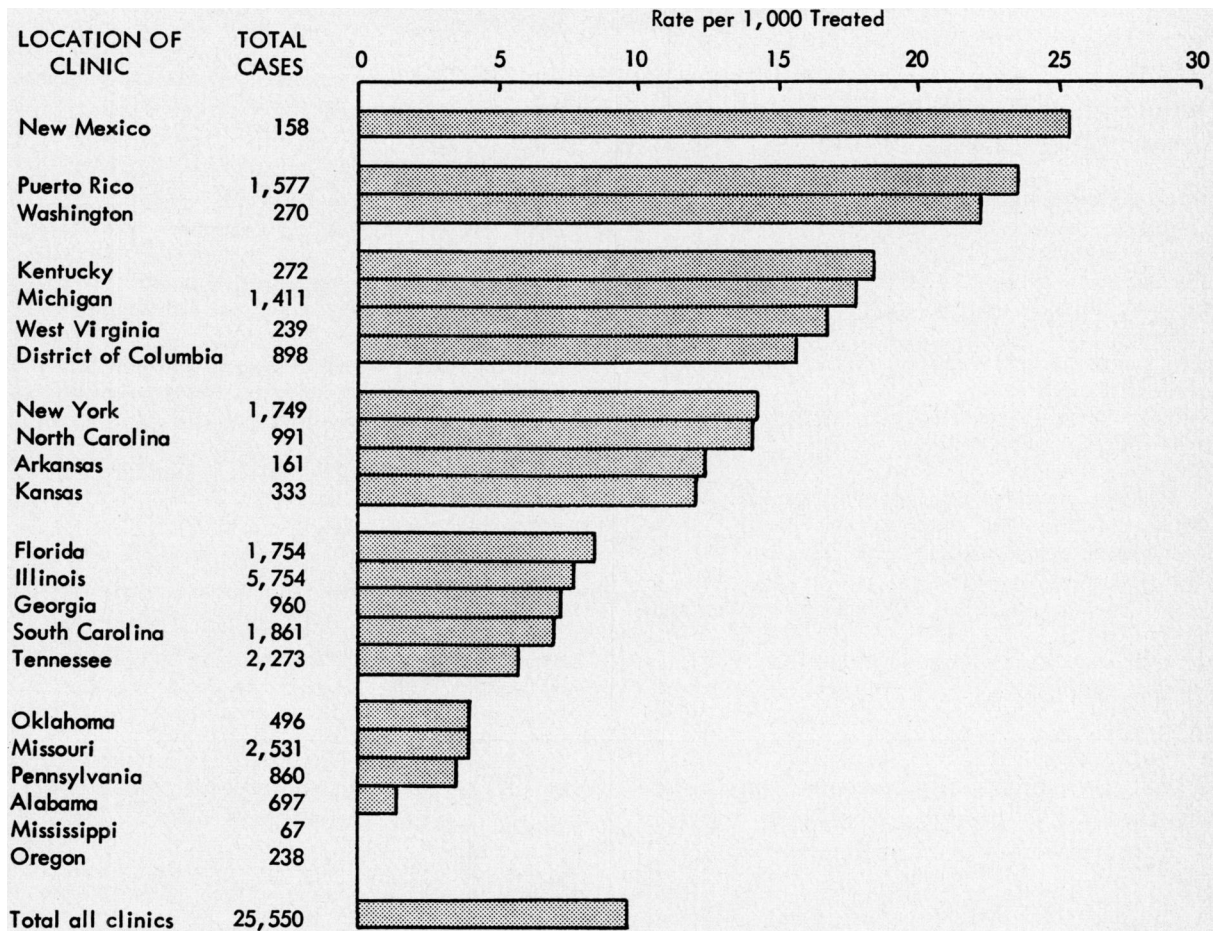
of reactions was less than 1 per 1,000 patients treated. In this group the principal reaction was syncope, which could be caused by fear of needle as readily as by penicillin. No anaphylactoid reactions were observed. The group treated at the centers is composed solely of Mexican male laborers who were given a single injection of 2,400,000 units of benzathine penicillin G. Since the men depart on contracts on the day of treatment, only immediate reactions, or those occurring within a few hours after injection, could be observed. The reluctance of the braceros to report an illness for fear of rejection has been offered by the medical officer in charge as a possible explanation for the almost complete absence of reactions. However, severe anaphylactoid reactions would be difficult to conceal.

Many other factors may have a bearing on the low incidence of reactions. Since the braceros are screened in Mexico, those reaching the reception centers are physically fit for strenuous labor. They may also represent a group less sensitized to penicillin. Certainly few are subjected to the almost continual penicillin therapy administered to chronic repeat-

Table 1. Frequency of reactions in venereal disease clinics and border reception centers

Type of penicillin reaction	Clinics		Border reception centers		All sources	
	Number cases	Rate per 1,000	Number cases	Rate per 1,000	Number cases	Rate per 1,000
Total cases treated.....	25,550		9,946		35,496	
Total cases reacting.....	248	9.71	7	0.70	255	7.18
Urticaria.....	146	5.71			146	4.11
Anaphylaxis.....	27	1.06			27	.76
Moderate to severe.....	9	.35			9	.25
Mild.....	18	.70			18	.51
Serum sickness.....	11	.43			11	.31
Other:						
Vertigo, syncope.....	25	.98	5	.50	30	.85
Generalized pruritus.....	23	.90			23	.65
Gastrointestinal (nausea, vomiting, abdominal pain).....	18	.70	1	.10	19	.54
Chills, fever, headache.....	14	.55	1	.10	15	.42
Angioneurotic edema.....	6	.23			6	.17
Dermatitis medicamentosa.....	4	.16			4	.11
Chest pain, dyspnea.....	3	.12			3	.08
Erythema multiforme.....	1	.04			1	.03
Dermatophytid.....	1	.04			1	.03
Hysteria.....	1	.04			1	.03
Jarisch-Herxheimer.....	1	.04			1	.03
Dysphagia.....	1	.04			1	.03
Unspecified.....	1	.04			1	.03

Figure 1. Comparative incidence of reactions by location of clinic



ers in venereal disease clinics. Only 50 percent gave a history of previous penicillin treatment, consisting principally of the injection received the previous year when crossing the border. Because of the seasonal nature of the program large numbers of braceros are treated in a short span of time, making it unlikely that drugs remain on the shelf very long.

Whatever the reasons, it is obvious that the two groups, braceros at the border reception centers and persons treated at venereal disease clinics, are not comparable. The following discussion, therefore, is limited to data from venereal disease clinics.

There was considerable variation among clinics, reaction rates ranging from 0 to more than 25 per 1,000 patients treated (fig. 1). Factors such as the number of cases treated, the amount and duration of treatment, and post-treatment observation period contributed to this variation.

For example, at the clinic in New Mexico which reported 4 reactions among 158 patients treated (25.3 per 1,000), the routine treatment for syphilis is 9,600,000 units covering a period of 3 weeks; at the clinic in Alabama which reported 1 reaction among 697 patients treated, a single injection of 2,400,000 units is routine for syphilis.

Schedules and Type of Penicillin

The effect on the incidence of reactions of total dosage and duration of schedule is shown in figure 2. The treatment shown is the planned schedule, not necessarily the amount the patient received prior to the occurrence of the reaction. In general, the longer the planned schedule of treatment and the larger the amount of penicillin, the greater the number of reactions reported. The longer schedules, of course, af-

Participating Agencies

Cooperating in the 1959 study to evaluate penicillin reactions among venereal disease patients were the following health departments and border reception centers of the Foreign Quarantine Division, Public Health Service.

Alabama: Montgomery County.

Arkansas: Pulaski County.

District of Columbia: District of Columbia.

Florida: Dade County, Duval County.

Georgia: Bulloch County, Chatham County, Fulton County, Macon-Bibb County, Muscogee County, Richmond County, Ware County.

Illinois: Chicago.

Kansas: Kansas City, Wichita-Sedgwick County.

Kentucky: Louisville-Jefferson County.

Michigan: Detroit.

Mississippi: Harrison County, Scott County.

Missouri: Kansas City, St. Louis.

New Mexico: Bernalillo County.

New York: New York City.

North Carolina: Charlotte, Durham County, New Hanover County.

Oklahoma: Oklahoma City.

Oregon: Portland.

Pennsylvania: Philadelphia.

Puerto Rico: Aguadilla, Arecibo, Barceloneta, Bayamón, Caguas, Cataño, Cayey, Fajardo, Guayama, Humacao, Juana Díaz, Manatí, Mayagüez, Ponce, Río Piedras, San Juan, Santurce, Vieques, Yabucoa.

South Carolina: Aiken County, Anderson County, Charleston County, Clarendon County, Georgetown County, Greenville County, Richland County, Spartanburg County.

Tennessee: Davidson County, Hamilton County, Memphis-Shelby County.

Washington: Seattle-King County.

West Virginia: Kanawha-Charleston, Logan County, Mercer-Bluefield, Mingo County.

The border reception centers were those at Nogales, Ariz., El Centro, Calif., and three in Texas at Eagle Pass, El Paso, and Hidalgo.

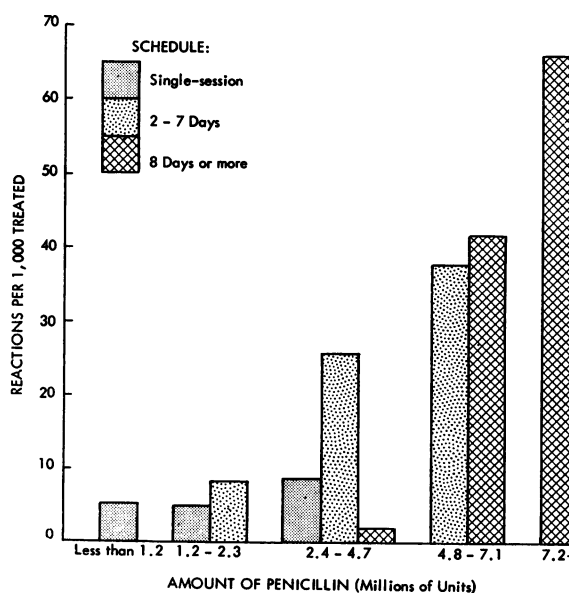
forded an opportunity for reactions to be observed. An exception to this is found in the group given 2.4 to 4.7 million units in schedules of 8 or more days' duration. This group, which had the lowest rate, was composed principally of women (presumably prostitutes) who were administered two 1,200,000-unit injections 2 weeks apart for prophylactic purposes. On the whole, this is a selected group with a demonstrated tolerance to penicillin.

Among patients treated on single-session schedules, the reaction rate was approximately the same for schedules of less than 1,200,000 units and for schedules of 1,200,000 to 2,300,000 units. However, the rate almost doubled for schedules of 2,400,000 to 4,700,000 units. For schedules of 2-7 days' duration the incidence of reactions ranged from 8.4 per 1,000 patients treated with 1,200,000 to 2,300,000 units to 38.0 per 1,000 treated with 4,800,000 to 7,100,000 units. Correspondingly large increases in reaction rates were observed with increased dosage in schedules of 8 or more days' duration.

PAM (procaine penicillin G with 2 percent aluminum monostearate) and benzathine penicillin G are the drugs of choice in venereal dis-

ease clinics. These two preparations, singly or combined, were administered to 94 percent of the patients included in the study. An additional 3.4 percent were treated with PAB, a

Figure 2. Incidence of reactions by amount of penicillin and duration of schedule



preparation containing both procaine penicillin G and benzathine penicillin G. Only 2.3 percent of the patients were treated with aqueous procaine penicillin G.

The incidence of reactions by type and amount of penicillin is shown in table 2. The type of penicillin plays a relatively unimportant role in the incidence of reactions. Where significant differences are observed, they can usually be explained on the basis of single-session therapy as opposed to treatment of longer duration. For example, in schedules of less than 2,400,000 units, benzathine penicillin G, either alone or combined with PAM, had a significantly lower reaction rate than aqueous procaine penicillin G (3.7 and 4.4 compared with 12.0 per 1,000); however, 98 percent of the benzathine penicillin G was administered in a single session as compared with only 59 percent of aqueous procaine penicillin G. In the 2,400,000 to 4,700,000 unit range, the lowest reaction rate (3.9 per 1,000) followed combined PAM and benzathine penicillin G therapy, 99

percent of which was administered in a single session, usually for gonorrhoea, in a total dosage of 2,400,000 or 2,700,000 units. None of the aqueous penicillin, which in this dosage range had a rate of 28.3 per 1,000, was administered in a single session; 93 percent was given in three injections for a total of 3,600,000 units. For the larger dosage schedules, no significant differences were observed among the types of penicillin employed.

Among the many factors thought to influence the incidence of reactions is sensitization of the population to penicillin. In countries such as the United States, some minor illnesses have been treated with penicillin, and there is ample opportunity for exposure to penicillin through dairy products and other foods. This almost universal exposure may account for the similarity of reaction rates among patients who gave no history of previous penicillin treatment and those who were previously treated without incident. The reaction rates for all patients in these two groups were 9.1 per

Table 2. Incidence of reactions by type and amount of penicillin

Type of penicillin	Millions of units			Total
	Less than 2.4	2.4-4.7	4.8 or more	
PAM (procaine penicillin G in oil and 2 percent aluminum monostearate):				
Number cases.....	8, 187	509	1, 598	10, 294
Cases reacting.....	49	6	67	122
Rate per 1,000.....	5.99	11.79	41.93	11.85
Benzathine penicillin G:				
Number cases.....	3, 505	1, 821	838	6, 164
Cases reacting.....	13	23	38	74
Rate per 1,000.....	3.71	12.63	45.35	12.01
Benzathine penicillin G and PAM:				
Number cases.....	6, 309	1, 277	29	7, 615
Cases reacting.....	28	5	2	35
Rate per 1,000.....	4.44	3.92	68.97	4.60
PAB (procaine penicillin G and benzathine penicillin G):				
Number cases.....	152	689	19	860
Cases reacting.....	1	6	0	7
Rate per 1,000.....	6.58	8.71	0.00	8.14
Aqueous procaine penicillin G:				
Number cases.....	418	106	65	589
Cases reacting.....	5	3	2	10
Rate per 1,000.....	11.96	28.30	30.77	16.98
All other:				
Number cases.....	23	3	2	28
Cases reacting.....	0	0	0	0
Rate per 1,000.....	0.00	0.00	0.00	0.00
All types:				
Number cases.....	18, 594	4, 405	2, 551	25, 550
Cases reacting.....	96	43	109	248
Rate per 1,000.....	5.16	9.76	42.73	9.71

1,000 for the untreated and 9.0 per 1,000 for the treated; 3.0 and 4.8 per 1,000 for treatment of less than 2,400,000 units; 8.6 and 10.1 per 1,000 for 2,400,000 to 4,700,000 units; and 40.3 and 39.4 for treatment of 4,800,000 units or more.

For all patients who had shown sensitivity to penicillin previously, the reaction rate was 117 per 1,000. Fifty-six of the 154 patients who gave a history of penicillin sensitivity were administered an antihistamine concomitantly with the penicillin, and only 1 in the group had further difficulty. This precautionary measure was not taken with the remaining 98 patients, and 17 experienced another reaction.

Race, Sex, and Age

The incidence of reactions varied according to the race, sex, and age composition of the population under study. The patients of the venereal disease clinics reporting in this study are principally Negro, with the majority under 30 years of age. These are the patients who showed the least sensitivity to penicillin (table 3 and fig. 3). Race is a more important factor than sex. The incidence of reactions was approximately the same in white males and in white females, but significantly greater

in Negro females than in Negro males. Both white males and white females had a greater incidence of reactions than Negroes of either sex.

Age as a factor is somewhat more difficult to appraise since it is directly related to diagnosis and hence to treatment. In general, the younger patients were treated for gonorrhea on low dosage schedules; the older patients for syphilis on high dosage schedules. The significant increase in incidence of reactions with increasing age (from 4.5 per 1,000 aged 10-19 years to 32.7 per 1,000 aged 50 and over), observed for the total, is almost eliminated when amount of treatment is considered (fig. 3). The only differences greater than could be attributed to chance are found in the 2,400,000- to 4,700,000-unit treatment group in which patients aged 40-49 years had a significantly higher incidence of reactions than patients aged 10-19 or 20-29 years.

Diagnosis

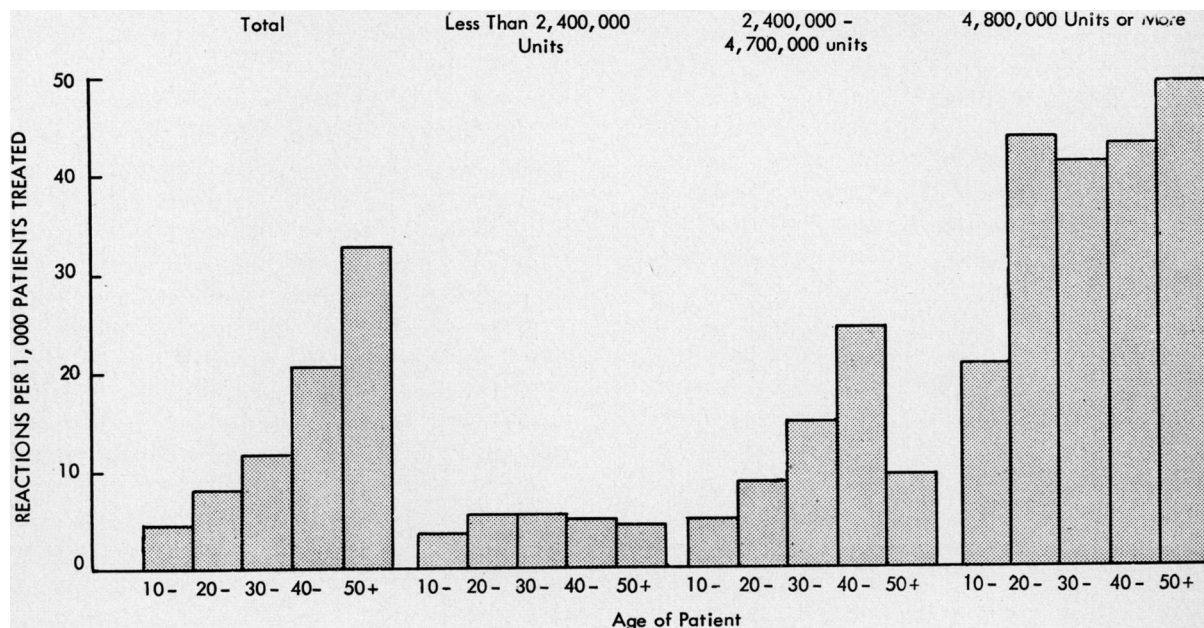
In planned schedules of less than 2,400,000 units, 94 percent of the 18,594 patients were treated for gonorrhea or as contacts to patients with gonorrhea. The incidence of reactions

Table 3. Incidence of reactions by race and sex and scheduled amount of penicillin

Race and sex	Millions of units			Total
	Less than 2.4	2.4-4.7	4.8 or more	
White male:				
Number cases.....	1, 166	180	200	1, 546
Cases reacting.....	9	3	12	24
Rate per 1,000.....	7. 72	16. 67	60. 00	15. 52
White female:				
Number cases.....	832	168	121	1, 121
Cases reacting.....	6	3	7	16
Rate per 1,000.....	7. 21	17. 86	57. 85	14. 27
Negro male:				
Number cases.....	8, 843	1, 623	831	11, 297
Cases reacting.....	40	14	24	78
Rate per 1,000.....	4. 52	8. 63	28. 88	6. 90
Negro female:				
Number cases.....	6, 205	1, 713	784	8, 702
Cases reacting.....	29	20	35	84
Rate per 1,000.....	4. 67	11. 68	44. 64	9. 65
Total:				
Number cases ¹	18, 594	4, 405	2, 551	25, 550
Cases reacting.....	96	43	109	248
Rate per 1,000.....	5. 16	9. 76	42. 73	9. 71

¹ Includes cases with race and sex unspecified.

Figure 3. Incidence of reactions by age of patient and scheduled amount of penicillin



was 5.2 per 1,000 for gonorrhea cases and 4.6 per 1,000 contacts. In planned schedules of 4,800,000 units or more, 98 percent of the 2,551 cases were treated for syphilis and 43.1 per 1,000 experienced a reaction to penicillin. Only the 2,400,000- to 4,700,000-unit treatment group permits a comparison by diagnosis:

Treatment	Number treated	Number reacting	Rate per 1,000
Gonorrhea:			
Contacts.....	769	5	6.5
Patients.....	2,249	16	7.1
Syphilis:			
Contacts.....	425	5	11.8
Patients.....	710	14	19.7

The reaction rates for gonorrhea and for contacts to patients with gonorrhea were approximately the same, 7.1 and 6.5 per 1,000, respectively. Both were significantly lower than the rate for syphilis, 19.7 per 1,000. Although the rate for treatment of contacts for syphilis was slightly higher than for gonorrhea and slightly lower than for syphilis, the differences are no greater than would be expected through chance. The higher rate for syphilis than for gonorrhea still exists when the comparison is limited to treatment of 2,400,000 units administered in a single session (22 compared with 6 per 1,000). A possible explanation may

be that patients treated for syphilis are observed more closely following treatment than patients treated for gonorrhea.

Comparison of 1959 and 1954 Studies

Reactions to penicillin were reported in 5.95 per 1,000 patients treated in 1954 and in 9.71 per 1,000 treated in 1959, an increase of 63 percent. The 1954 study was similar in design to the 1959 study. However, the amount of penicillin in the planned schedule was not requested in 1954, nor were the clinics asked to detain patients in the clinic following penicillin injection. Since 1954 there has been a general increase in the penicillin dosage employed for gonorrhea, with the 600,000-unit routine being replaced at most clinics with a 1,800,000-unit schedule. In 1959, only 15 percent of the gonorrhea cases were treated with less than 1,200,000 units; 70 percent were treated with amounts ranging from 1,200,000 to 2,300,000 units, and the remaining 15 percent received 2,400,000 units or more. The incidence of reactions in these three treatment groups, however, was approximately the same, 6.7, 4.9, and 7.0 per 1,000, respectively. It is difficult, therefore, to attribute the increase in incidence of reactions in 1959 to the increased dosage for gonorrhea.

The two studies are compared by diagnosis and duration of planned schedule in table 4. Significantly higher rates in 1959 occur only for single-session schedules and for the total in each diagnostic group. The 30-minute detention period would have the most effect on the single-session schedules since most patients treated on such schedules are seldom seen following treatment and must be relied upon to report to the clinic if reactions occur. The differences between the two studies for schedules of 2 to 7 days and 8 to 14 days were no greater than could be expected through chance. For schedules for syphilis of more than 2 weeks' duration, the incidence of reactions was greater in 1954 than in 1959.

Further indication that the higher incidence of reactions in 1959 may be the result of the detention period is a comparison of the types of reactions observed in the two studies (table 5). Urticaria, the principal reaction, was reported with approximately the same frequency in both studies. Anaphylaxis was observed

more frequently in 1959 than in 1954. The difference was significant, however, only in those classified as mild. It might be explained that "moderate to severe" includes chiefly patients requiring hospitalization. Reports on two who were exceptions to this follow:

Case 1. "Approximately 30-45 seconds after injection patient became cold, clammy, perspiring, slightly cyanotic, and nauseated. Blood pressure fell to 70/0 but rose to 140/80 about 3 minutes after injection of 15 minims of epinephrine subcutaneous and 25 mg. of benadryl intravenous—and being placed in shock position. Discharged from the clinic 45 minutes later in good condition."

Case 2. "Within seconds after injection, patient collapsed. Pulse too rapid and feeble to count. Treated with oxygen by mask, adrenalin 0.3 cc. subcutaneous stat. Followed by some relief of symptoms. Given 100 mg. Solucortef intravenous and adrenalin 0.2 cc. subcutaneous. After 20 minutes blood pressure 120/80, pulse 70 and regular."

Table 4. Comparative frequency of reactions reported in 1959 and 1954 by diagnosis and duration of planned schedule

Diagnosis and duration of planned schedule	1959 study			1954 study		
	Total cases	Cases reacting		Total cases	Cases reacting	
		Number	Rate per 1,000		Number	Rate per 1,000
Contact treatment.....	5,938	32	5.39	3,757	10	2.66
Single-session.....	5,509	27	4.90	3,743	9	2.40
2-7 days.....	95	4	42.11	13	1	76.92
8-14 days.....	43		0.00	1		0.00
Over 14 days.....	291	1	3.44			
Gonorrhoea.....	15,104	83	5.50	12,026	29	2.41
Single-session.....	14,101	71	5.04	11,877	27	2.27
2-7 days.....	854	12	14.05	144	2	13.89
8-14 days.....	105		0.00	5		0.00
Over 14 days.....	44		0.00			
Syphilis.....	3,229	122	37.78	3,442	77	22.37
Single-session.....	622	13	20.90	1,993	15	7.53
2-7 days.....	815	29	35.58	350	11	31.43
8-14 days.....	1,099	61	55.51	637	25	39.25
Over 14 days.....	693	19	27.42	462	26	56.28
All diagnoses ¹	25,550	248	9.71	19,510	116	5.95
Single-session.....	21,502	122	5.67	17,710	51	2.88
2-7 days.....	1,768	45	25.45	694	14	20.17
8-14 days.....	1,252	61	48.72	644	25	38.82
Over 14 days.....	1,028	20	19.46	462	26	56.28

¹ Includes other and unspecified disease.

Table 5. Comparative frequency of various types of reactions to penicillin in 1959 and 1954

Type of penicillin reaction	1959 study		1954 study	
	Number	Rate per 1,000	Number	Rate per 1,000
Total cases treated	25,550	-----	19,510	-----
Total cases reacting	248	9.71	116	5.95
Urticaria	146	5.71	96	4.92
Anaphylaxis	27	1.06	4	.21
Moderate to severe	9	.35	4	.21
Mild	18	.70	-----	.00
Serum sickness	11	.43	5	.26
Other:				
Vertigo, syncope	25	.98	-----	.00
Generalized pruritus	23	.90	2	.10
Gastrointestinal (nausea, vomiting, abdominal pain)	18	.70	1	.05
Chills, fever, headache	14	.55	-----	.00
Angioneurotic edema	6	.23	-----	.00
Dermatitis medicamentosa	4	.16	5	.26
Chest pain, dyspnea	3	.12	2	.10
Erythema multiforme	1	.04	1	.05
Dermatophytid	1	.04	1	.05
Hysteria	1	.04	-----	.00
Jarisch-Herxheimer	1	.04	-----	.00
Dysphagia	1	.04	-----	.00
Unspecified	1	.04	-----	.00

Patients with reactions classified as mild anaphylaxis exhibited a combination of approximately three of the following symptoms: syncope, vertigo, profuse sweating, chills, weakness, dyspnea, constriction of chest, respiratory symptoms, abdominal cramps, nausea and vomiting, pruritus, flushing of skin, and angioneurotic edema. It will be noted that these same symptoms are listed as "other" reactions. These constitute a group in which it was felt that either singly or combined the symptoms did not warrant a diagnosis of anaphylaxis. These reactions and those classified as mild anaphylaxis were almost completely absent in the 1954 study.

Although undoubtedly there is a greater awareness today of the risk involved in penicillin treatment, which would account for an increase in the observation and reporting of

reactions, it is felt that the request in 1959 that clinics detain patients for 30 minutes following penicillin injection contributed in large measure to the increase. Reactions such as vertigo, syncope, dyspnea, and others, although of serious import to the clinician, are symptoms (usually transient in nature) which the average person would dismiss as too inconsequential to report. This is substantiated by the fact that 50 percent of the reactions reported in 1959 occurred on the first day of treatment, 30 percent within the first half hour. In 1954 only 16 percent of the reactions reported occurred on the first day.

Fatal Reactions

No deaths occurred at any clinic during its 3-month period of participation in the study. However, one of the clinics reported a fatal reaction which occurred in March 1960, the last month of the collection period. This was the only death in more than 100,000 patients treated by the cooperating clinics during the year.

The patient who died was a 23-year-old Negro man who was admitted to the clinic on March 16, 1960, with a diagnosis of anterior urethral gonorrhea. He had been treated for gonorrhea on November 12, 1959, and again on February 3, 1960, with 1,200,000 units of benzathine penicillin G without difficulty. On March 16 the patient was again given the same dose of this drug. In the next several minutes he complained of feeling ill and nauseated and attempted to vomit into the waste container. He then stood up, stating he felt better and continued dressing in order to leave. At this point the patient collapsed. His condition deteriorated rapidly, pulse and blood pressure were unobtainable, and the patient became unresponsive. Emergency therapy, administered immediately, consisted of oxygen, adrenalin injected intravenously and intramuscularly, and penicillinase given intramuscularly. The patient was pronounced dead approximately 40 minutes following treatment. Unfortunately an autopsy was not performed.

Fatal reactions among venereal disease patients are relatively infrequent, but as this case attests, they are an ever-present possibility. It cannot be too strongly recommended that

every treatment room where penicillin is administered, whether in clinic, hospital, or private physician's office, have in readiness for use at a moment's notice, supplies and equipment for any emergency which might arise. As an added precaution, the patient should be kept under observation following treatment as long as is practicable.

Summary and Conclusions

Sixty-four health departments in 21 States, the District of Columbia, and Puerto Rico and 5 border reception centers participated in a cooperative study to determine the present incidence of reactions to penicillin among patients treated for venereal diseases. During the study period 35,496 patients were treated with penicillin and reactions were reported in 255, or 7.2 per 1,000. More reactions were observed in venereal disease clinics than at the border reception centers, 9.7 as against 0.7 per 1,000. The reasons for this difference are discussed.

In venereal disease clinic patients urticaria was the most frequent reaction, occurring in 5.7 per 1,000. Anaphylaxis was observed in 27 (1.1 per 1,000) but in only 9 was it classified as moderate to severe. Serum sickness was reported in 11. No deaths occurred during the study period. The incidence of reactions varied by source of report from 0 to 25 per 1,000 patients treated.

In general, the longer the planned schedule of treatment and the larger the amount of penicillin, the greater the number of reactions observed. In single-session schedules of less than 1,200,000 units, the reaction rate was 5.3 per 1,000 compared with 66.1 per 1,000 in schedules of 7,200,000 units or more administered in a period of 8 or more days.

No difference in toxicity was observed between the two principal types of penicillin used in venereal disease clinics (procaine penicillin

G in oil with 2 percent aluminum monostearate and benzathine penicillin G). There was no evidence to indicate that patients are becoming sensitized to penicillin; the incidence of reactions was the same in patients who had never had penicillin therapy as in those who had been treated previously without incident. Reactions were frequent among patients who had shown sensitivity previously to penicillin, but in this group antihistamines appeared to reduce the risk.

Race was a more important factor than sex, with Negro patients tolerating penicillin better than white patients; age also appears to be a factor, with the incidence of reactions increasing with age.

The incidence of reactions was greater in 1959 than in 1954 when a similar study was conducted. It is believed that the increase was due to better observation of the patients rather than to increased sensitization to penicillin.

On the basis of these findings, no changes in the present treatment practices in venereal disease clinics are indicated. It is recommended that emergency supplies and equipment be kept in readiness and that patients be observed closely for immediate reactions following treatment.

REFERENCES

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Correction

In "Current Status of Syphilis in the United States," by William J. Brown, in *Public Health Reports*, November 1960, change the title of figure 2 on page 991 to read: "Figure 2. Total cases of syphilis reported by private physicians and clinics and hospitals, Pennsylvania, 1958-59."