The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 133, No. 10 CHICAGO, ILLINOIS MARCH 8, 1947

PENICILLIN THERAPY OF SCARLET FEVER

Comparison with Antitoxin and Symptomatic Therapy

HAROLD L. HIRSH, M.D.
GEORGINE ROTMAN-KAVKA, M.D.
HARRY F. DOWLING, M.D.
and
LEWIS K. SWEET, M.D.
Washington, D. C.

In a previous publication [1] we reported on the efficacy of intramuscular penicillin X in the treatment of 34 cases of scarlet fever. Since that time we have continued to treat this streptococcic infection with other types of penicillin and now wish to report similarly good results in the treatment of 86 patients, representing 52 patients in addition to the 34 in the original group.

PLAN OF STUDY

All the patients studied were on the isolation service of the Gallinger Municipal Hospital. Three criteria were established for the inclusion of a patient in this series: (1) temperature of 102 F. or over; (2) evidence of pronounced toxicity regardless of the height of the temperature, or (3) the presence of a pyogenic complication.

The ages of the patients ranged from 1 to 41 years, although 79 were less than 12 years of age. There were an equal number of males and females; 54 patients were Negroes. All but 6 patients had temperatures of 102 F. or over on admission. Three of these 6 patients had complicating infections of the skin, and the remaining 3 were decidedly toxic, although their temperature was recorded as less than 102 F.

The first 34 patients were treated with penicillin X [2] and the results have been reported elsewhere.[1] Most of the patients in this group received 50,000 units of the medicament every six hours, although early in the study several different dosage schedules were employed. Crystalline penicillin G [3] was employed in the next 5 patients. The dosage schedule established was 25,000 units every three hours. Thereafter we decided to compare the results of penicillin therapy with those of administration of scarlet fever antitoxin. Alternate patients were given either commercial penicillin in doses of 25,000 units every three hours or 9,000 to 27,000 units of antitoxin, depending on the degree of toxicity. Sulfadiazine was given to the patients receiving antitoxin when there were evidences of a pyogenic complication. Twenty-nine patients were treated with penicillin and 25 received antitoxin. Four additional patients who received antitoxin were later eliminated from the series because the evidence was inadequate for the diagnosis of scarlet fever. Seven patients received sulfadiazine in addition to antitoxin. A final group of 18 patients were treated with oral penicillin, prepared in tablets containing 25,000 units buffered with calcium carbonate.[4] Since it has been recommended that three to ten times the parenteral dose be given for oral administration, we decided to administer five times our established parenteral dose, or 125,000 units, every three hours.

The duration of treatment is extremely important in the therapy of beta hemolytic streptococcic infections with penicillin. Plummer and his associates [5] showed that the incidence of relapse was high in patients treated for hemolytic streptococcic pharyngitis unless penicillin therapy was continued for four to six days. Our early experience with the use of penicillin in these infections confirmed this observation. We therefore established five days as a minimum period of treatment for scarlet fever. In 3 patients therapy was continued for two to four days longer because of the persistence of complications which had been present on admission. Three patients were given only a single injection of 100,000, 200,000 and 300,000 units, respectively, of penicillin X as a part of an investigation of the absorption and effect of large doses of this penicillin fraction.

Throat cultures on blood agar plates were taken on admission on all patients before treatment was begun, daily thereafter for five days and then at two to three day intervals until the patient was discharged. Some of the streptococci were typed according to the slide agglutination method of Griffith through the courtesy of Mr. J. N. Adam of the Lederle Laboratories, Inc.

RESULTS

The results of treatment of scarlet fever with penicillin were evaluated on the basis of the following criteria: (1) the time required for the temperature to fall and remain below 99 F. rectally, exclusive of fever due to complications; (2) the incidence of pyogenic complications developing after admission, and (3) the number of patients who were found to have beta hemolytic streptococci in their throats after the start of therapy. In table 1 are shown the results of treatment with the various preparations of penicillin. It can be seen that the response was essentially the same irrespective of the preparation and route of administration employed.

From the George Washington University Medical Division and the Infectious Disease Service, Gallinger Municipal Hospital, and the Departments of Medicine and Pediatrics, George Washington University School of Medicine.

1. Hirsh, H. L.; Dowling, H. F., and Sweet, L. K.: Treatment of Various Infections with Penicillin X, with a Preliminary Note on the Value of Penicillin X in Scarlet Fever, Ann. Int. Med. **25**: 78 (July) 1946.
2. Supplied by the Lederle Laboratories, Inc., Pearl River, N. Y.
3. Supplied by Merck & Co., Rahway, N. J.
4. Supplied by the Lederle Laboratories, Inc., Pearl River, N. Y.
5. Plummer, N.; Duerschner, D. R.; Warren, H. D.; Rogliano, F. T., and Sloan, R. G.: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, J. A. M. A. **127**: 369 (Feb. 17) 1945.

The various types of temperature response following penicillin therapy are depicted in charts 1, 2 and 3. Most patients had a rapid drop in temperature as shown in chart 1, while in a few the return of the temperature to normal was more prolonged (charts 2 and 3). The average duration of fever following the start of therapy was calculated for each group and found to range from forty-nine to fifty-four hours. The average for the group receiving penicillin X does not include 2 patients, 1 of whom had a normal temperature on admission and was treated because of the presence of an infected finger and another who failed to respond to penicillin therapy. In the case of the latter patient, the administration of penicillin was continued without effect for seventy-two

TABLE 1.—*Comparison of the Results of Treatment of Scarlet Fever with Various Types of Penicillin*

Type of Penicillin Employed	Route of Administration	No. of Patients	Average Duration of Fever Following First Dose of Penicillin, Hrs.	No. of Patients Who Developed Pyogenic Complications After Admission	No. of Patients in Whom Throat Cultures Positive for Hemolytic Streptococci Recurred After the Completion of Therapy
X	Intramuscular	34	54	3	4
Crystalline G	Intramuscular	5	52	0	0
Commercial G	Intramuscular	29	50	3	3
Commercial G *	Oral	18	49	0	0
All patients		86	52	6	7

* Buffered with calcium carbonate.

TABLE 2.—*Comparison of the Results Against Scarlet Fever in Patients Treated Symptomatically with Penicillin or with Antitoxin*

Method of Treatment	No. of Patients	Average Duration of Fever *	Incidence of Bacterial Complications After Administration	Incidence of Throat Cultures Positive for Hemolytic Streptococci During Convalescence
Commercial penicillin G †..	29	50	10%	10%
Antitoxin †	25	29	44%	85%
All types of penicillin	86	52	7%	8%
Symptomatic	123	99	26%	82%

* Calculated from the time of the first dose of penicillin or antitoxin or from the time of admission to the hospital in symptomatically-treated patients.
† Treated in alternation.

hours, whereupon she was given 18,000 units of antitoxin with prompt improvement. Further study revealed that the type 14 hemolytic streptococcus isolated from her throat was resistant to the concentrations of penicillin found in her blood. The details are shown in chart 4.

In 6 patients pyogenic complications developed following the start of therapy. Two patients who had received single injections of 200,000 and 300,000 units of penicillin X developed recurrent pharyngitis on the third and seventh hospital days, respectively. The first patient was given another injection of 200,000 units with rapid improvement, and the second recovered on symptomatic measures. The course of the second of these patients is shown in chart 5. Three patients, 1 treated with penicillin X and 2 with commercial penicillin, had recurrent pharyngitis on the fourteenth to twenty-first days after penicillin therapy was discontinued, following their exposure to fresh cases of scarlet fever. These 3 patients recovered within forty-eight hours on symptomatic therapy. In the sixth patient there developed a temperature of 101 F., which persisted

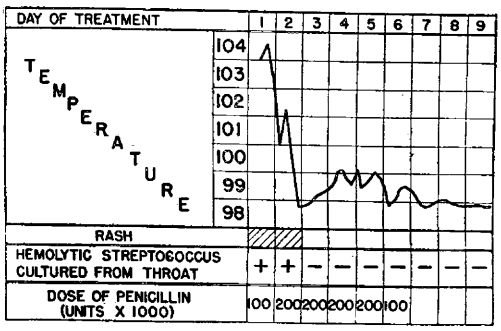

Chart 1.—E. H., Negro girl aged 3.

for forty-eight hours and for which no cause could be determined. Although pyogenic complications occurred only in the groups of patients treated with penicillin X and commercial penicillin, the number of patients treated with oral or crystalline penicillin G intramuscularly was too small to lend significance to the absence of complications. In 3 patients there developed sequelae, namely, rheumatic fever, acute nephritis and serous meningitis.

Among the 86 patients treated with penicillin, a beta hemolytic streptococcus was isolated from the throats of 75 on admission. The throat cultures were free of the organism in each instance within forty-eight hours after treatment was started. Only 5 patients who were adequately treated had a return of the beta hemolytic streptococcus while under observation, which was usually for a twenty-one day period. Three of those patients were exposed to fresh cases of scarlet fever on the fourteenth to twenty-first day after treatment was discontinued. Type 14 beta hemolytic streptococci were isolated from the cultures of material from the throats of the patients at the time of the recurrence as well as on admission. The contacts were found to have the same type of streptococci. The remaining 2 patients

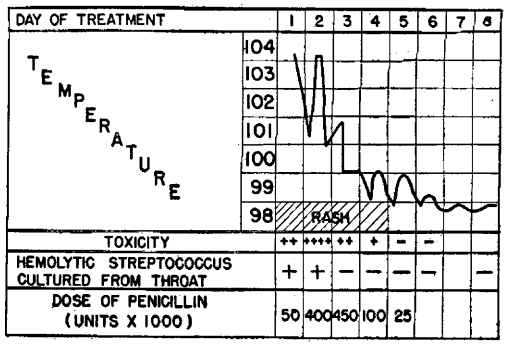

Chart 2.—I. D., Negro girl aged 8.

were found to have type 4 and type 19 streptococci in their throats on their eighteenth and nineteenth days of hospitalization, which persisted until their discharge on the twenty-first hospital day. Types 8 and 14 streptococci, respectively, had been isolated on admission from the cultures of material from the throats of these 2 patients. The 2 patients who had relapses

after inadequate penicillin therapy were found to have type 17 streptococci on admission and at the time of the relapse. The organisms disappeared from the throat cultures of 1 of these patients following an injection of 200,000 units of penicillin and from those of the other, who was treated symptomatically, after eight days. The effect of penicillin on the pharyngeal flora was independent of the type of penicillin employed or the method of administration.

Although only 18 patients have been treated with oral penicillin in comparison to 68 patients treated by the intramuscular route, in the small group the results were equally as good as in the patients treated parenterally. It must be borne in mind, however, that the oral dose was five times as great as the parenteral.

COMPARISON OF THE RESULTS OF PENICILLIN THERAPY, ANTITOXIN AND SYMPTOMATIC THERAPY

In table 2 we have listed the results of treatment with penicillin as compared with antitoxin on the basis of the three criteria established for the evaluation of therapy. It can be seen that the average duration of fever after the administration of antitoxin was twenty-nine hours as compared to fifty hours for the penicillin-treated patients. Of the 29 patients treated with

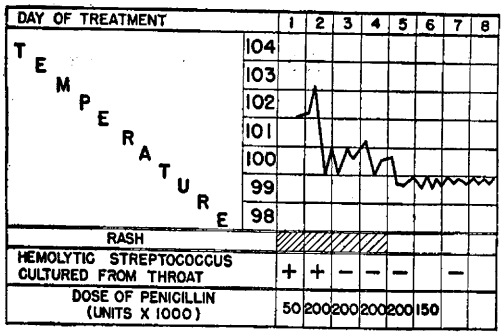

Chart 3.—D. D., white boy aged 14.

penicillin, only 3 (10 per cent) had mild pyogenic complications consisting of mild pharyngitis on the fourteenth to twenty-first days after the completion of therapy. These complications can probably be accounted for on the basis of exposure to fresh cases of scarlet fever. Further treatment was not required, and the patients were improved within seventy-two hours after the onset of the recurrence. On the other hand, in 11 of the 25 patients (44 per cent) given antitoxin there developed pyogenic complications, consisting of 7 cases of otitis media, 2 cases of cervical adenitis and 2 cases of recurrent pharyngitis. All these patients were given sulfonamide therapy. Moreover, while only 10 per cent of the penicillin-treated patients had a return of hemolytic streptococci late in their hospital stay, 85 per cent of a similar group of patients treated with antitoxin continued to have the organisms in their throat for the greater part of the observation period of three weeks. The advantages of penicillin in preventing the carrier state are obvious.

Meads and his associates [6] have reported on the treatment of 9 patients with 15,000 units every four hours for seven days. These investigators concluded that penicillin eliminated the hemolytic streptococcus carrier state and prevented complications due to this organism but that it did not influence the eruption and toxic manifestations of scarlet fever. We have compared the course of scarlet fever in 86 patients treated with penicillin with the course in 123 patients who were given only symptomatic therapy because the disease was considered too mild for additional treatment (table 2). The incidence of complications was 7 per

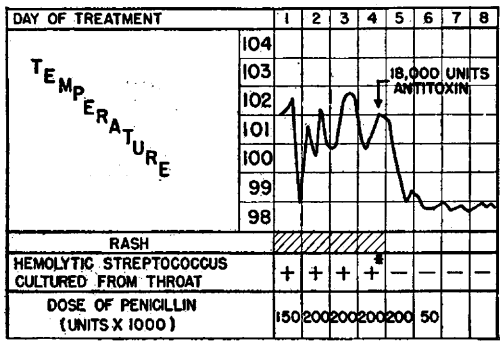

Chart 4.—E. H., Negro boy aged 4. * Hemolytic streptococcus sensitive to 0.625 unit of penicillin. The highest blood concentration equaled 0.156 unit of penicillin.

cent in the penicillin-treated group compared with 26 per cent in the group treated symptomatically. The streptococcic carrier rate before discharge from the hospital was 8 per cent in the former and 82 per cent in the latter group. These results are in accord with the observations of Meads and his associates,[6] but in addition we found that penicillin reduces the toxicity and hastens the disappearance of the eruption. The average duration of fever was fifty-two hours in the patients treated with penicillin compared with ninety-nine hours in the group treated symptomatically. The decrease in toxicity paralleled the fall in temperature. Although the character of the rash in scarlet fever is exceedingly variable and difficult to evaluate, we were convinced that in the majority of instances the rash disappeared more rapidly in the penicillin-treated group of patients.

COMMENT

Although penicillin has been found to be highly bactericidal for the beta hemolytic streptococcus, the question of whether the various types of the antibiotic would be equally effective in the treatment of scarlet fever had to be determined. On treating 86 patients, we found that penicillin decreased the toxicity, greatly diminished the incidence of pyogenic complications and practically eliminated the carrier state.

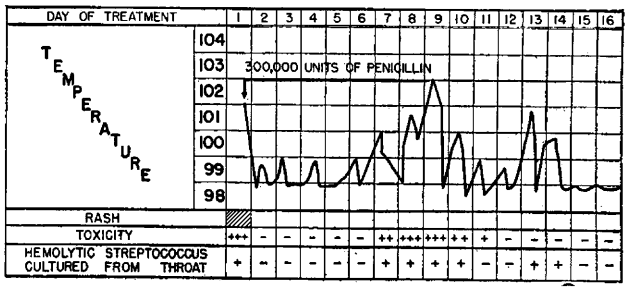

Chart 5.—M. D., white woman aged 29.

Our second problem was to determine a practicable dosage schedule. The administration of 25,000 units intramuscularly or 125,000 units orally of penicillin G every three hours for five days was found to be an adequate regimen for the great majority of patients. Fifty thousand units of penicillin X every six hours were equally efficacious. All but 1 of the patients

6. Meads, M.; Flipse, M. E.; Barnes, M. W., and Finland, M.: Penicillin Therapy of Scarlet Fever, J. A. M. A. **129**: 785 (Nov. 17) 1945.

treated according to these dosage schedules recovered uneventfully. Since the hemolytic streptococcus isolated from the throat of this patient was a more resistant organism, it is probable that the patient would have responded to penicillin had she received larger doses. The need for at least five days of treatment is demonstrated by the fact that 2 of 3 patients treated for shorter periods relapsed.

The results obtained by Epidemiology Unit no. 82, United States Naval Hospital, Treasure Island [7] were similar to ours. In patients treated for three days and receiving a total dose of 240,000 units, the incidence of pyogenic complications was 31 per cent and the recurrence of positive throat cultures was 77 per cent. When patients were treated for six days with 360,000 units the figures were 14 per cent and 27 per cent, respectively. Complications occurred in only 6 per cent of the patients and recurrence of positive throat cultures in only 8 per cent when treatment consisted of 480,000 units given during an eight day period. This group of investigators employed small doses consisting of 10,000 units every three to six hours.

The third problem was to compare the results of penicillin and antitoxin therapy. For this purpose two groups of patients were treated with each agent in strict alternation. The incidence of pyogenic complications in the group treated with penicillin was 10 per cent, compared with 44 per cent in the antitoxin-treated group, and the incidence of positive throat cultures after the start of therapy was 7 per cent and 85 per cent, respectively, for the two groups. On the other hand, the temperature took nearly twice as long to fall to normal in the penicillin-treated group as in the antitoxin-treated patients. Although this difference appears well defined, observations of the patients demonstrated that both groups felt as well within the same period of time. Usually the fall in temperature after the administration of antitoxin was precipitous. The fall in temperature following the initiation of penicillin therapy was generally rapid, but frequently there were slight elevations for a day or two, during which time the patients appeared and felt relatively well. It was these small spikes in temperature which prolonged the figures for the average duration of fever as determined by our criteria.

There were other apparent advantages of penicillin over antitoxin. Fourteen patients treated with penicillin entered the hospital with preexisting complications such as otitis media, cervical adenitis and infections of the skin. All recovered uneventfully from both the scarlet fever and the complication coincident with the use of penicillin. Several of these patients were treated for two to four days longer than the time prescribed for the treatment of the scarlet fever because of the relatively slower improvement of the complication. Penicillin obviated the need for sulfonamide drugs, which were administered to the patients treated with antitoxin who had evidence of pyogenic complications.

A further advantage of penicillin over antitoxin in the routine treatment of scarlet fever is the elimination of the frequent occurrence of serum sickness following the use of antitoxin. Among the 25 patients treated with antitoxin in the present study, for instance, 3 manifested serum sickness, whereas none of the 86 patients receiving penicillin showed any symptoms of hypersensitivity to this antibiotic.

Ashley [8] has reported that penicillin plus antitoxin is superior to antitoxin alone. We are unable to evaluate these observations because we did not employ the two agents in combination. It appears from our results that adequate penicillin therapy is sufficient for the treatment of most patients with scarlet fever. An occasional patient who is critically ill with this disease, however, will undoubtedly require antitoxin as well as penicillin. Based on our experience with 1 patient who failed to respond to penicillin, it would appear that any patient who does not improve after forty-eight hours of antibiotic therapy should be given larger doses of penicillin on the presumption that the streptococcus is relatively resistant to penicillin and probably should receive antitoxin also.

From a comparison of the results of penicillin therapy and symptomatic therapy of scarlet fever, it would appear prudent to treat mild cases of this disease with penicillin to reduce the incidence of pyogenic complications, which in themselves may be serious problems, even though the toxicity is not sufficient to require the use of penicillin.

Now that the value of penicillin in the treatment of scarlet fever has been established, one might conjecture as to the mode of action. Two of us [9] have shown that penicillin does not neutralize the erythrogenic toxin of the hemolytic streptococcus. Since penicillin in adequate concentrations is bactericidal for penicillin-sensitive organisms, it appears that this antibiotic brings about rapid disappearance of the beta hemolytic streptococci and thus eliminates the source of the erythrogenic toxin. The small amount of toxin already formed by the bacteria is apparently neutralized by the defenses of the body.

At present, we would recommend that all patients with scarlet fever be given penicillin intramuscularly in doses of 25,000 units every three hours of commercial or crystalline penicillin G or in doses of 50,000 units every six hours of penicillin X, or orally in doses of 125,000 units of commercial penicillin G every three hours. Severely toxic patients should receive antitoxin in addition. Penicillin therapy should be continued for at least five days, or until the patient has recovered from all pyogenic complications.

SUMMARY AND CONCLUSIONS

1. Eighty-six patients with scarlet fever have been treated with penicillin X, crystalline penicillin G and commercial penicillin.

2. Penicillin therapy resulted in a prompt fall in temperature, a decrease in toxicity and a decided reduction in the incidence of pyogenic complications and of the carrier state.

3. Penicillin was more effective than antitoxin or symptomatic therapy in the prevention of complications and in reducing the number of carriers and was equally as effective in decreasing toxicity. Antitoxin caused a more rapid decline in temperature than did penicillin. On the other hand, the temperature dropped more rapidly in patients given penicillin than in symptomatically-treated patients.

7. Observations on the Treatment of Scarlet Fever with Penicillin, Epidemiology Unit Number 82, Am. J. M. Sc. **217**: 417 (April) 1946.

8. Ashley, P.: Treatment of Scarlet Fever, J. A. M. A. **130**: 771 (March 23) 1946.

9. Dowling, H. F., and Hirsh, H. L.: The Inability of Penicillin to Inactivate the Dick and Schick Toxins, Proc. Soc. Exper. Biol. & Med. **63**: 163 (Oct.) 1946.

ADDENDUM

Since this paper was submitted for publication an additional 50 patients have been treated with 100,000 units of penicillin administered every four hours orally. The fall in temperatures and the decrease in toxicity were prompt. In none of the patients did there develop a pyogenic complication, and the beta hemolytic streptococcus disappeared during therapy in each instance.

PENICILLIN FOR SCARLET FEVER

ARCHIBALD L. HOYNE, M.D.
and
ROWINE HAYES BROWN, M.D.
Chicago

Almost from the moment penicillin became available for therapeutic purposes its value in the treatment of streptococcic infections was acknowledged.[1] For that reason we believed it desirable to determine if penicillin would be an efficient agent in the treatment of scarlet fever. We considered that it ought to be helpful in combating scarlet fever regardless of whether the disease was mild or severe. Consequently, during the past fourteen months we have used penicillin as an exclusive therapeutic agent for 116 patients with scarlet fever.

Since beginning our observations on the action of penicillin in scarlet fever, Meads, Flipse, Barnes and Finland [2] have published a report concerning 9 patients with scarlet fever who were treated with penicillin. Ashley [3] stated recently that the treatment of choice for scarlet fever consists in giving both convalescent scarlet fever serum and penicillin. But on the basis of past experience we believe equally good results may be obtained by the use of convalescent scarlet fever serum alone.[4] Other clinicians [5] have reported success with the sulfonamide compounds. However, in our opinion sulfonamide drugs are not of value in overcoming the toxemia of scarlet fever. Our primary purpose in making this study was not to demonstrate whether penicillin was more effective than sulfonamide compounds or convalescent scarlet fever serum against scarlet fever, but to decide if any beneficial response from the use of penicillin could be shown. On that account, we administered only penicillin to one group of patients and to other groups gave a single therapeutic agent for comparison.

Between Jan. 1, 1945 and March 1, 1946, 548 patients with scarlet fever were admitted to Municipal Contagious Disease Hospital. Of that number, besides the 116 who were given penicillin, 69 were treated with convalescent scarlet fever serum, 48 with one of the sulfonamide drugs and 2 with scarlet fever antitoxin; the remaining 312, who were given neither serum nor drug, served as controls. Owing to the fact that scarlet fever antitoxin was used only twice, these 2 instances are excluded from further consideration. Likewise, the single fatality among the 548 admissions is not included in any of the groups, because the patient concerned had received convalescent scarlet fever serum before she entered the hospital. However, we treated her with penicillin, but she died as the result of hepatitis and pericarditis which were present at the time of admission.

No criterion was followed in regard to selection of the remedies employed. Therefore we feel that some comparison of the different groups is justified for the following reasons: (1) all patients were treated in the same hospital in a given period of time; (2) in each group there were mild, moderate and severe instances of the disease, and (3) evaluations in respect to treatment were based on the impressions formed by the same observers through personal contact and study. Before analyzing the several groups it should be stated that scarlet fever in Chicago has been unusually mild during the past few years. This last fact is emphasized by the occurrence of only 1 death in our total series of 548 patients. Possibly a more informative comparison could have been made of the various methods of treatment if the disease had been of greater virulence.

TABLE 1.—*Forms of Scarlet Fever and of Treatment*

	Mild	Moderate	Severe	Total
Penicillin	52	55	9	116
Convalescent serum	44	23	2	69
Sulfonamide compounds	37	11	0	48
Control	200	110	2	312
Total	333	199	13	545

TABLE 2.—*Averages Relating to Days Ill, Duration of Fever and Duration of Rash*

		Average			
	Patients	Days Ill on Admission	Temperature on Admission	Duration of Fever After Admission	Duration of Rash
Penicillin	116	3.86	101.69 F.	3.46	2.93
Convalescent serum	69	2.98	101.9 F.	3.49	3.42
Sulfonamide compounds	48	3.5	100.88 F.	2.98	3.04
Control	312	3.2	100.88 F.	2.60	3.44

In table 1 the patients are classified according to the severity of the illness and are grouped in respect to the form of therapy administered. The number of mild cases was about 4 to 5 times greater among the controls than in any of the other groups. This fact is reflected by the low percentage of complications occurring in the control group. A somewhat similar situation exists in respect to the patients whose disease was classified as moderate. The number of severe cases was too small to permit any thoroughly satisfactory conclusions. In the various groups there was no special selection of patients either according to age or sex. Although the ages ranged from 7 months to 41 years, most patients were children. The average for all ages was 8.2 years. There was an almost equal division in respect to sex.

In table 2 the 548 patients are divided according to both method of treatment and average number of days ill at the time of admission. Although the average number of days ill was higher for the penicillin treated group, there is no sharp difference in the corresponding averages of the other groups. These averages suggest that the prognostic expectancy for patients in the group given penicillin would be the least favorable.

Again in table 2 it may be seen that the average range of temperature at the time of hospitalization varied but

From Municipal Contagious Disease Hospital, Chicago Health Department.

1. Fleming, A.: On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of Bacillus Influenza, Brit. J. Exper. Path. **10**: 226-236 (June) 1929. Abraham, E. P.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G., and Jennings, M. A.: Further Observations on Penicillin, Lancet **2**: 177-188 (Aug.) 1941. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, B., Jr.: Penicillin in the Treatment of Infections, J. A. M. A. **122**: 1217-1224 (Aug. 28) 1943.

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