

## THE TREATMENT OF LOBAR PNEUMONIA AND PNEUMOCOCCAL EMPHYEMA WITH PENICILLIN\*

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THE therapeutic value of penicillin for patients was first described in the treatment of cases of staphylococcal infection.<sup>1</sup> Even though penicillin has not been found in tests in the laboratory to be as potent in antibacterial action against staphylococci as against pneumococci or hemolytic streptococci, it is, nevertheless, more effective against staphylococci than are the sulfonamide drugs. Consequently, the fact that clinical trials were first attempted in cases of severe staphylococcal sepsis constituted a rational procedure and subsequent experience has yielded highly satisfactory results in this type of infection that has not been uniformly amenable to sulfonamide therapy.<sup>1,2,3</sup>

In accord with experimental studies which have demonstrated the antagonistic action of penicillin against a wide variety of pathogenic bacterial species, estimates of the value of penicillin therapy have been broadened beyond cases of staphylococcal etiology to include many different kinds of infection in man. The most recent results have been recorded and summarized in the comprehensive report of Keefer, Blake, Marshall, Lockwood, and Wood.<sup>3</sup>

The present report is limited to a description of the results obtained in the treatment of pneumococcal pneumonia and pneumococcal emphyema with penicillin.

The unusually high degree of antibacterial activity of penicillin, *in vitro*, against pneumococci was demonstrated in the original report of Fleming<sup>4</sup> and has been repeatedly observed by others.<sup>5,6,7</sup> *In vivo*, the curative action of penicillin in mice has been demonstrated against many

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hundred thousand lethal doses of highly virulent strains of different serological types of pneumococci.<sup>8,9</sup> Although some variation in the sensitivity of strains has been suggested, pneumococci appear to be one of the pathogenic bacterial species most vulnerable to the action of penicillin.

When the experimental results just mentioned are taken into account in connection with the proven low toxicity of penicillin for man, the favorable outcome of the treatment of pneumococcal infections with penicillin becomes a reasonable expectancy.

Forty-six cases of pneumococcal pneumonia and 8 cases of pneumococcal empyema comprise the present series. In view of the fact that the methods of treatment and the details of the study of the cases of pneumonia and of the cases of empyema were different, each of the subjects is presented separately.

#### I. THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH PENICILLIN

Although the number (46) cases of pneumonia is not great, the selection of patients to be treated with penicillin was limited to those who, on admission, exhibited lobar consolidation and a degree of severity indicating the probable pneumococcal etiology of the infection. Even though therapy was at times instituted before the bacteriology was reported there were only three instances in which the specific etiology was undetermined. The data in Table I on the distribution of serological types of pneumococci responsible for the infections and also the incidence of bacteriemia indicate that the cases used for treatment consisted of a representative sample of pneumococcal pneumonia with respect to kind and severity.

In the patients with pneumonia the observations have been directed not only toward determining the value of penicillin as an effective curative agent but the attempt has also been made to estimate the range of dosage that was sufficient without constantly employing amounts that might be excessive and, therefore, unnecessary. For this latter purpose the number of injections and the duration of treatment were arbitrarily altered in order to observe the response to limited treatment.

*Material and Route of Administration.* The penicillin was supplied in a dry powder contained in sealed ampoules. It was kept constantly in the ice box. Solutions for injection when prepared in advance were also kept in refrigeration but were not retained for longer than a day

or two. It may be noted in passing that solutions used in the laboratory for experimental purposes have been found to retain potency for several weeks.

Penicillin in solution was given to patients by repeated injections either intravenously or intramuscularly. For intravenous injection the powder was dissolved in physiological salt solution or sterile water in the ratio of 1000 units to 1-1.5 cc. of solution. For intramuscular injection the ratio was 1000 units to 0.3 cc. of solution so that the usual individual dose of 10,000 units was contained in a total volume of 3.0 cc.

Some of the patients were treated solely by intravenous injections, others only by intramuscular injections, and still others received intravenous medication for the first few doses followed by intramuscular injections for subsequent treatments. The intramuscular route proved to be effective and was, for convenience sake, frequently employed. However, in cases which appeared seriously ill on admission, one to four injections were given intravenously and when improvement seemed evident subsequent injections were given intramuscularly.

*Dosage of Penicillin and Spacing of Treatment.* The amount of penicillin per dose ranged from 10,000 to 25,000 units, most frequently the former. The repeated doses which were given in series were made at three hour intervals.

Several procedures were employed which differed in the following respects:

1. Number of repeated injections at three hourly intervals which comprised one series of treatments. The single series varied from three to eight injections, the latter lasting for twenty-four hours.

2. The lapses between each series of injections which were given from day to day were not always kept constant. Charts are presented which illustrate the clinical courses of patients who received interrupted treatment.

3. The number of consecutive days of treatment varied from one to four. The information which emerged from altering the duration of treatment will be subsequently discussed.

*Etiological Pneumococcal Types.* From Table I it may be noted that in 32 (69 per cent) of the cases the infecting pneumococci belonged to serological Types I-VIII. Fourteen patients had bacteriemia (30 per cent). Among the cases in which the pneumonia was due to pneumococci, Types I-VIII, 13 (40 per cent) has bacteriemia.

TABLE I  
SUMMARY OF CASES OF PNEUMONIA TREATED WITH PENICILLIN

Pneumo Types	No. of Cases	Blood Culture	Duration of Treatment Days				Total Dosage of Penicillin (Range) Oxford Units	Response		Died
			1	2	3	4		Definite	Indefinite	
I	11	4	7	2	5	3	60,000-250,000 Av: 148,000	10		1
II	6	3	3	1	3	2	70,000-170,000 Av: 113,000	6		
III	1	1	0		1		140,000	1		
IV	1	1	0		1		110,000	1		
V	5	1	4	1	2	2	70,000-190,000 Av. 115,000	4	1	
VII	2	1	1	1		1	70,000-140,000 Av: 105,000	2		
VIII	4	2	2		2	1	70,000-120,000 Av. 90,000	3		1
IX	1	0	1		1		120,000			1
XI	2	0	2	1		1	40,000-130,000 Av: 85,000	2		
XII	1	0	1		1		90,000	1		
XV	1	0	1		1		120,000	1		
XIX	1	0	1		1		90,000	1		
XX	1	1	0	1			50,000	1		
XXIX	1	0	1		1		95,000			1
Unclass.	7	0	7	2	1	3	30,000-160,000 Av: 100,000	5	2	
TOTAL	45	14	31	4	7	21	30,000-250,000 Av. 105,000	38	4	3

*Outcome of Treatment.* Among the 46 patients treated with penicillin, three died. (Mortality 6.5 per cent). Of the patients who died, one was a 69 year old man who had severe congestive heart failure together with pneumonia and bacteriemia due to pneumococcus, Type VIII. His blood culture, taken on the second hospital day, was sterile and his temperature was below 100°F. but the heart failure was worse. He died 36 hours after admission. The second fatal case had pneumonia and bacteriemia, pneumococcus, Type I, superimposed on some chronic pulmonary disease. His blood culture of the second hospital day was sterile but there was no clinical improvement. Subsequent therapy included sulfadiazine and antipneumococcus serum, Type I, but it was ineffectual. The third fatal case had pneumonia due to pneumococcus, Type I, but no bacteriemia. He did not appear severely ill but did not respond to penicillin. He died on the third hospital day a few hours after pulmonary edema developed.

Of the 43 patients who recovered, in four instances therapy was not followed by rapid clinical recovery. The result is, therefore, listed as indefinite, although the final diagnosis in one patient was primary atypical pneumonia and the other three had prolonged courses, in one of whom there was delayed resolution which was unexplained; in another, who after several weeks developed pneumothorax, tuberculosis was suspected; and the third patient had bronchiectasis on which the pneumonia was superimposed. Even though these three latter cases are classed as ineffectively treated, the sterilization of the bacteriemia by penicillin in two of them will be subsequently mentioned.

The remaining 39 patients (84 per cent) recovered in a manner that indicated the high degree of effectiveness of penicillin.

The rapidity in the drop in temperature was striking, the change occurring usually within the first 12 to 20 hours, and the impression was that the response occurred somewhat more quickly than that observed after sulfonamide therapy. The alleviation of symptoms was marked. The respirations were slowed to normal rates coincident with improvement although cough persisted for several days. There were no untoward depressive physiological reactions referable to the rapid critical change in the condition of the patients. Although no data have been collected with regard to the rate with which clearing of the consolidated area occurred, the impression has been formed that resolution progressed more rapidly than that observed following sulfonamide therapy.

The leukocyte count was unaffected by penicillin and returned to normal within four to six days.

No toxic reactions were observed, except an occasional pyrogenic reaction which came on about one hour after an injection and lasted approximately two hours. The degree of soreness at the site of intramuscular injection was never severe, nor was there any swelling or redness or appreciable local irritation.

The hematopoietic system exhibited no signs of irritation. No special changes in urine were noted. No psychic or neurological abnormalities were evident.

*Duration of Treatment.* From an analysis of the data given in Table I under the heading "Duration of Treatment, Days," information is available concerning the length of time that therapy may be required. In all of the patients without complications an initial definite response was noted within 16 to 20 hours of beginning treatment as evidenced by sharp drop in temperature and symptomatic improvement. The subsequent course varied, however, depending on the length of time treatment was continued.

From Table I it may be seen that most of the patients, 31, were treated for 3 to 4 days. Among this group, when no complicating factors existed, the initial improvement persisted as permanent cure.

The complications which delayed prompt and complete recovery were empyema and chronic pulmonary disease on which pneumonic consolidation was superimposed. Among the cases with complications other than empyema it may be stated that when treatment was switched to sulfadiazine no appreciable response was obtained.

*Clinical Response in Relation To Dosage.* In attempting to estimate the amount of penicillin necessary to suppress the infection, the injections in selected patients were arbitrarily interrupted after the first or second day of treatment. Most of the patients in these groups received 30,000 to 40,000 units per day in divided doses of 10,000 units each. The reaction of the infection to the measured treatment has served as a source of information with regard to the degree and duration of the response in relation to quantity of the drug.

Table II contains data derived from patients in whom injections of penicillin were arbitrarily withheld following either one or two days of therapy. An analysis of the material in Table II reveals the following:

In each of the seven cases in which penicillin therapy was adminis-

TABLE II  
COURSE OF PATIENTS IN WHOM ADMINISTRATION OF PENICILLIN  
WAS INTERRUPTED AFTER ONE OR TWO DAYS OF THERAPY

Patient	Admin. Day of Disease	Pneumonia Type	Blood Culture	Penicillin—1st Day		Penicillin—2nd Day		Initial Response	Subsequent Course
				No. of Injections	Daily Amount	No. of Injections	Daily Amount		
J. Z.	3rd	Unclassi- fied	—	3	30,000	—	—	Yes	Rapid Recovery
M. H.	3rd	VII	—	3	30,000	—	—	Yes	Relapse
D. R.	2nd	Unclassi- fied	—	4	40,000	—	—	Yes	Rapid Recovery
V. J.	2nd	XI	—	4	40,000	—	—	Yes	Rapid Recovery
B. M.	3rd	II	—	4	40,000	—	—	Yes	Relapse
F. T.	?	XX	+	5	50,000	—	—	?	Prolonged
J. G.	3rd	VIII	—	7	70,000	—	—	?	Died
L. T.	4th	II	—	4	40,000	3	30,000	Yes	Rapid Recovery
A. K.	3rd	V	—	6	60,000	3	30,000	Yes	Relapse?
J. B.	5th	II	—	4	40,000	4	40,000	Yes	Relapse?
A. L.	3rd	Unclassi- fied	—	4	40,000	3	30,000	Yes	Relapse
E. F.	1st	II	+	4	40,000	5	50,000	Yes	Relapse
M. B.	4th	V	+	4	40,000	5	25,000	Yes	Empyema
O. B.	?	I	+	3	30,000	3	30,000	?	Died

tered on the first day and then interrupted, there was a significant drop in temperature to below  $101^{\circ}$  in 16 to 24 hours but permanent cure was not uniformly effected.

In each of the two patients in the one day group with bacteriemia a second blood culture taken on the second hospital day was sterile.

With the exception of the patient who died 36 hours after admission, symptomatic improvement accompanied the early fall in temperature.

Complete cure followed a single series of injections given for one day in three cases. However, it should be noted that the pneumococci isolated from their sputum belonged to serological types not usually associated with severe pneumonia. Consequently, the mildness of the pneumonia may have promoted the striking response even though the patients were treated early in the disease, i.e., 3rd, 2nd and 2nd days respectively.

In the three remaining cases who recovered and in whom treatment was withheld after the first day, a relapse of the infection occurred. Recovery, however, promptly followed the reinstatement of treatment.

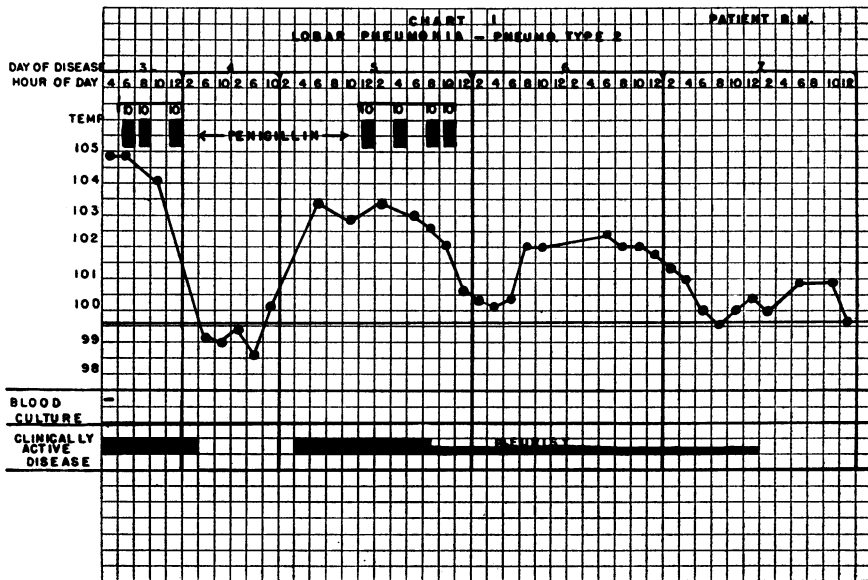
In the patients who were treated on *two consecutive days* before withholding therapy, with the exception of the fatal case, improvement followed the first day of therapy. Consequently, the second series of injections was given after improvement had begun. In each instance of bacteriemia in this group, the blood culture taken on the second day was sterile and remained so.

As to the final outcome following two days of treatment one of the patients made a rapid and permanent recovery, whereas, among the remaining cases in this group, two had transient rises of fever to  $101^{\circ}$  to  $102^{\circ}$  appearing 48 hours after the last injection and spontaneously receding within two days, and the other two had definite relapses.

From a consideration of the findings given in Table II it appears that penicillin in the dosages employed evoked rapid early improvement indicating the high degree of sensitivity of the infecting pneumococci to penicillin. It is also evident that relapse was liable to occur if treatment was not extended longer than two days.

From the standpoint of chemotherapy the importance of the development of type specific immunity in promoting permanent recovery from pneumococcus infections has been illustrated both experimentally and clinically in relation to sulfonamide therapy. MacLeod<sup>10</sup> demon-



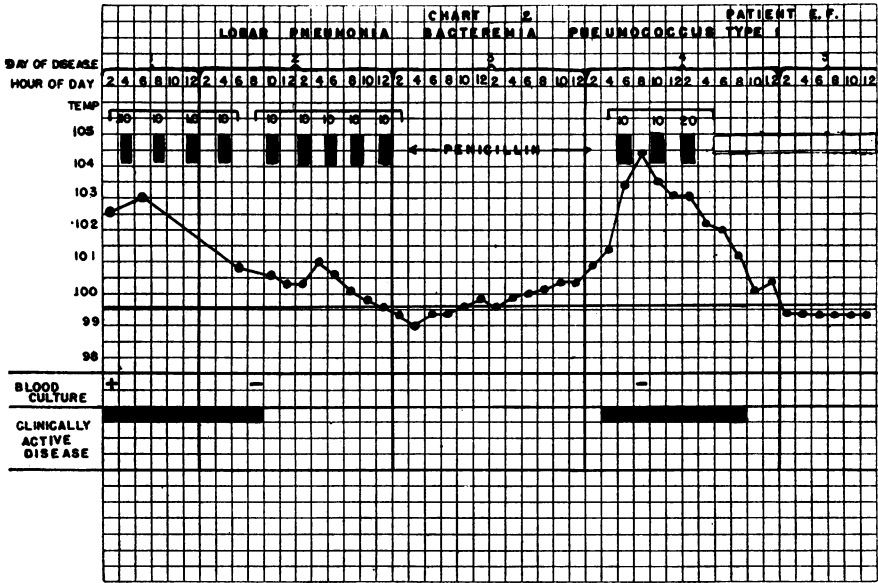


strated in mice that the suppression of pneumococcal infection by sulfa-pyridine was made permanent by the appearance of type specific immunity. In pneumonia the observation has been repeatedly made that patients treated early (first to third day) with appropriate sulfonamides are liable to relapse if treatment is stopped in one or two days.

In comparing the experience with sulfonamides with that encountered with penicillin it seems probable that the continuance of treatment as determined by the day of disease is of equal importance with either of the drugs.

For purposes of demonstrating graphically the quantitative relationships between dosage and its effect on the infection with particular reference to the duration of the remission after premature withdrawal of treatment, the details of the courses of two patients are given in Charts 1 and 2.

Chart 1 is that of a patient with pneumonia due to pneumococcus, Type II, who was admitted on the 3rd day of disease. Following the details of the temperature chart it may be seen that the last dose of penicillin on the first day was given at approximately 12 midnight and that the temperature became normal between 2 and 6 the following morning—12 hours after beginning therapy. That the therapeutic effect



was not solely antipyretic is evidenced by the marked alleviation of symptoms during the afebrile period. The patient became worse at about 4 o'clock on the morning of the 3rd hospital day, approximately 28 hours after the last injection. In view of the fact that measurable amounts of penicillin have been found by Rammelkamp and Keefer<sup>11</sup> to disappear from the blood within 3 hours after injection, the disease in this patient was restrained for approximately 25 hours after the blood level of penicillin was presumably zero.

The second series of injections of penicillin given on the 3rd hospital day was also followed by a definite response. A dry pleurisy persisted for two additional days but complete recovery was not further delayed.

Chart 2 is that of a patient whose course was particularly instructive. He was admitted eight hours after a chill which initiated the attack of pneumonia. Injections of penicillin were begun promptly. His blood culture was positive for pneumococcus, Type 1. His course illustrates the importance of taking into account the day of disease on which therapy is begun in determining the duration of therapy. In this patient two series of injections on two consecutive days were given before withdrawal of treatment. His response to the first four injections of the first

day occurred, as indicated in Chart 2, within 16 hours. A second blood culture taken five hours after the last previous injection of penicillin was sterile. The initial early improvement was maintained for approximately 28 hours after treatment was stopped. A relapse then occurred abruptly, although a blood culture taken at the height of the febrile exacerbation was negative.

Penicillin therapy was again instituted on the fourth day. Subsequently in this case sulfadiazine was given as supplementary treatment during the latter part of the fourth day because the patient was encountered early in the trials of penicillin before its efficiency for pneumonia had been well established. Permanent recovery occurred on the 6th hospital day.

The course of the two patients just described, in addition to illustrating the rate of response, also demonstrates the duration of the period of remission after premature interruption of treatment.

Results comparable to those just described have been observed in other patients who were followed in a similar manner. In summary, they indicate that, in the average uncomplicated case of pneumonia, the administration of 30,000 to 40,000 units per day in divided doses initiates improvement. Furthermore, the remission evoked by the therapy endured for approximately 20 to 28 hours before the effect of the penicillin was lost.

These findings have afforded useful information in formulating a complete course of treatment with respect to quantity and spacing of dosage.

Additional data of a similar character have been derived from an analysis of the course of the patients with bacteriemia in relation to the injections of penicillin which they received.

*Effect of Penicillin on Bacteriemia.* Fourteen of the patients had bacteriemia on admission. In each instance following penicillin therapy the second blood culture was sterile. In seven of the patients the time relationships between the second blood culture and the last previous dose of penicillin is sufficiently definite to offer information concerning the duration of the sterilizing effect. The findings are contained in Table III.

The quantitative range of dosage during the first 24 hours in this particular group of bacteriemic cases was from 30,000 to 105,000 units. The differences in amounts of penicillin that were administered oc-

TABLE III  
AMOUNT OF PENICILLIN EFFECTIVE IN ALTERING BACTERIEMIA\*

Pneumo Type (Patient)	1st Blood Culture	Amt. of Penicillin before 2nd Bl. Culture Units	Route of Administration	2nd** Blood Culture	Interval between previous dose of Penicillin and 2nd Blood Culture
I (J. S.)	+	105,000	75,000 Intravenous 30,000 Intramuscular	—	3 hrs.
I (J. St.)	+	90,000	25,000 Intravenous 65,000 Intramuscular	—	5 hrs.
II (M. L.)	+	60,000	Intravenous	—	6 hrs.
II (E. F.)	+	40,000	Intravenous	—	9 hrs.
III (B. R.)	+	40,000	Intravenous	—	5 hrs.
VIII (J. G.)	+	60,000	Intravenous	—	16 hrs.
I (O. B.)	+	30,000	Intravenous	—	10 hrs.

\*In the six other cases which had bacteriemia on admission the 2nd blood culture was sterile, but it was not taken until the 2nd or 3rd day of hospitalization.

\*\*In each instance the 2nd blood culture was taken approximately 20-24 hours after the 1st.

curred for the most part in connection with explorations of dosage which was altered as experience developed. That the blood stream was cleared in each instance is striking evidence of the potency of penicillin in its antipneumococcal action.

It is of further interest to note from Table III the time of the last previous dose of penicillin in relation to the time of taking blood for the second culture. From the figures in the table it may be seen that intervals of from 3 to 16 hours elapsed but that the bacteriemia did not return. By the method which they employed, Rammelkamp and Keefer<sup>11</sup> found that penicillin was detectable in the blood for 30 to 210 minutes after intravenous injection, the time varying according to the dosage of the drug. On the basis of the figures of these authors, it may be estimated that, in the bacteriemic patients described in Table III, the initial clearing of the blood was maintained in different patients for varying periods of time up to at least 13 hours after circulating penicillin was presumably no longer detectable. Consequently, the damaging effect of penicillin on the invasive pneumococci appears to have restrained their regrowth for an appreciable period after the blood level ceased to be measurable.

Each of the patients of Table III received penicillin intravenously. Whether the rapidity and persistence of the clearing of the blood of pneumococci is best accomplished by intravenous medication has not been determined since comparable studies have not been made following intramuscular injections. The findings in the bacteriemic cases when combined with the results illustrated in the previous Tables and Charts suggest that the maintenance of a definite level of penicillin continuously may not be a necessary detail of satisfactory treatment.

#### DISCUSSION OF FACTORS INVOLVED IN THE APPLICATION OF PENICILLIN TO THE TREATMENT OF PNEUMONIA

*Duration of Treatment.* On the basis of the experience described in this article it seems apparent that in order to avoid relapses, treatment should be extended over three or four days or for longer periods under special conditions. As stated earlier the duration of treatment is influenced by the day of the disease on which it is started since a remission effected early in the infection (first to third day) may not be maintained unless treatment is continued until the elements of immunity or other factors in the evolution of the disease become operative.

With regard to continued repetitions of injections the data have indicated that when an interval of 12 to 16 hours was permitted to elapse between daily treatments the results were as satisfactory as those obtained by maintaining therapy throughout 24 hours. The special studies demonstrate that the arrest of the infection caused by penicillin was continued beyond the period during which penicillin would be expected to be detectable in the circulating blood.

The reports of Florey and associates<sup>1</sup> and of Rammelkamp and Keefer<sup>11</sup> have described the rapid excretion of penicillin in the urine and also the distribution of the drug in normal body fluids following parenteral injection. However, the extent to which penicillin penetrates into inflamed areas, or the concentration or the persistence of the product in an active state in the extravascular sites of the infection within tissues has not been determined. Whether or not alterations in permeability and diffusion which membranes undergo as a result of inflammation affect the dissemination of penicillin has not been determined.

In interpreting the protracted effect by which the abatement of the infection persisted after the disappearance of circulating penicillin, it seems possible that the result may be dependent upon the retention of penicillin at the local site of the infection for a longer period of time than in the circulating blood, or that the damage inflicted by temporary contact between penicillin and pneumococci is sufficiently severe to delay the further multiplication of organisms.

On the basis of the response of patients, therefore, four injections daily at three hour intervals on three to four successive days has proved satisfactory.

*Route of Injection.* For the cases of relatively moderate severity, the intramuscular route of injection has been found to be efficacious. However, in patients appearing seriously ill or in those with bacteriemia, the results following intravenous therapy as measured by clinical improvement and disappearance of bacteriemia (Table III) indicate the effectiveness of the intravenous route, which may be preferable for the first few injections.

*Amounts per Dose.* 10,000 units have been the routine amount employed for intramuscular injection. 10,000 or 25,000 units have been given in intravenous injections, depending on the severity of the case.

*Suggested Plan of Treatment.* Consolidating the findings that have

been discussed above, the following procedure is tentatively outlined.

**Cases of Moderate Severity:** 10,000 units of penicillin given intramuscularly every three hours for four doses on each of three and possibly four successive days.

**Seriously Ill Cases:** 25,000 units given intravenously every three hours for the first two doses of the first day, followed by 10,000 units intramuscularly at three hour intervals for the second two doses of the first day. Subsequent treatment of the second, third, and fourth day to follow plan outlined for cases of moderate severity, i.e., four doses of 10,000 units every three hours for each day.

It is obvious that variations in the clinical course of individual cases may require special alterations in treatment. It should also be emphasized that the above suggestions are not presented as established recommendations but that they represent a current appraisal based on the objective data contained in this report. In view of the low toxicity of penicillin, more extensive therapy than that outlined may be employed without the hazards of serious reactions. However, this study has been directed toward an attempt to define quantitatively the relation of clinical response to therapeutic dosage.

*Comparative Value of Penicillin and Sulfadiazine in Pneumonia.* Our experience indicates that the therapeutic value of penicillin in pneumonia is at least equal to that of sulfadiazine, and, in addition, there are certain well defined conditions that make the use of penicillin particularly advantageous. They may be summarized as follows:

1. The fact that, up to the present time, no significant toxic manifestations have been noted in association with the administration of penicillin is of special interest. A few cases of urticaria have been described<sup>9</sup> (none in the present series) but the evidence is inconclusive that the eruptions were based on the development of sensitivity. It is furthermore, uncertain whether such reactions were caused by penicillin or by some contaminating ingredient present in the preparations.

2. Penicillin is particularly serviceable when pre-existing sensitivity to the sulfonamide drugs contraindicates their use, or when sulfonamide toxicity develops during treatment before the infection has been completely overcome.

3. Penicillin has been shown experimentally to be highly effective against sulfonamide-fast pneumococci.<sup>9, 12, 13</sup> In the second part of this article which deals with the local use of penicillin in the treatment of

empyema, the value of penicillin in patients suffering from infections caused by sulfonamide-resistant pneumococci will be described.

It is also of interest to record briefly the favorable response to penicillin of two patients with lobar pneumonia and bacteriemia due to pneumococci refractory to sulfadiazine.

One of the patients in the present series was admitted to the hospital on the seventh day of pneumonia after having received sulfadiazine continuously from the beginning of his illness but without improvement. On admission, in addition to lobar consolidation, he also had bacteriemia due to pneumococcus, Type VII, and a blood level of sulfadiazine of 6.6 mgms. per cent which remained from the pre-admission treatment. By laboratory tests the strain derived from the blood culture proved to be sulfonamide-fast.

Under penicillin therapy the blood culture became sterile within 24 hours and the patient recovered uneventfully in spite of the fact that he also had lymphatic leukemia.

A second instance of infection with a sulfonamide-resistant strain of pneumococcus successfully treated with penicillin was that of a 63-year-old female\* who had had pneumonia and an intermittent bacteriemia due to pneumococcus, Type VIII, for approximately 4 weeks before penicillin therapy was instituted. Early in her disease she also developed empyema which was treated surgically by rib resection and drained satisfactorily. She had received sulfadiazine continuously for 4 weeks without permanently altering the bacteriemia. She had also received Type VIII antipneumococcus serum with only temporary improvement. There were no definite signs of endocarditis. On the day following the first injection of penicillin her blood became sterile and remained so. The pneumonia subsided.

In laboratory tests the pneumococci from both the blood culture and the empyemal pus were found resistant to sulfadiazine.

4. Although as yet unsubstantiated by objective data, it seems likely that penicillin sterilizes the blood stream in cases of bacteriemia and suppresses the active infection at a more rapid rate than does sulfadiazine. Although in many instances this difference may not be of special significance, nevertheless in cases of unusually severe infection, the speed of effect may be particularly desirable.

\* This case was under the care of Dr. Robert C. Schleussner at the Lenox Hill Hospital and is reported with his permission.



Even though the use of penicillin has the definite advantages just mentioned, the extent to which its widespread use in large numbers of cases of pneumonia would markedly alter mortality statistics is not clear. Analyses of causes of death in cases of pneumonia treated with the sulfonamide drugs<sup>14</sup> have brought out the fact that the majority of the fatalities are due to a variety of complicating circumstances that would not in themselves be overcome even by a more potent anti-pneumococcal drug.

## II. THE TREATMENT OF PNEUMOCOCCAL EMPYEMA BY THE INTRAPLEURAL INJECTION OF PENICILLIN

This study of pneumococcal empyema has been directed toward determining the possible usefulness of chemotherapeutic agents introduced locally as a medical method of treatment which might obviate surgical intervention. In spite of the fact that there seems to have been a decrease in the incidence of empyema caused by pneumococci since the introduction of chemotherapy for pneumonia, the administration of the sulfonamide drugs either by mouth or intravenously has not proved satisfactory in the treatment of empyema after the complication has developed.

At the beginning of the present inquiry observations were made on the course of empyema following the intrapleural injection of sulfadiazine. As a curative measure the initial attempts were unsatisfactory since the pneumococci causing the pleural infections were found to retain viability in the presence of large amounts of the drug and the patient's illness remained unchanged. Consequently, penicillin was employed for local injection.

Up to the present time eight patients with pneumococcal empyema have been treated by the introduction of solutions of penicillin into the infected pleural space. The empyemata, with one possible exception, developed as a complication of lobar pneumonia.

Although the details of this report deal with the efficacy of penicillin introduced locally into the empyemal cavities, before proceeding with a description of the methods and results, it is of interest to record briefly some of the observations which were made in connection with local sulfonamide therapy.

The findings are illustrated by the course of one of the patients who was first treated with sulfadiazine and later with penicillin injected

intrapleurally (See Chart 3). After the introduction of sulfadiazine into the empyemal cavity of this patient the sulfonamide content of the exudate reached 415 mgms. per cent. However, on examination of the exudate, pneumococci were seen in direct smears and were viable on culture.

In seeking an explanation for the inactivity of the drug against the organisms as exemplified in the case just mentioned, tests were made for the presence of sulfonamide inhibitors in samples of empyemal exudate obtained from this and other patients. Experiments were also carried out to determine the degree of sulfonamide fastness possessed by several strains of pneumococci derived from empyemal pus.

The results may be briefly summarized as follows:

1. Estimation of the presence of sulfonamide inhibiting substances in pneumococcal pus from cases of empyema.

Five different specimens from four different patients were tested. The method described by MacLeod<sup>15</sup> was employed using a strain of *B. coli* which was cultivated in an inhibitor-free medium in the presence of varying quantities of sulfadiazine. Exudate was then added and its effect on growth observed. The results obtained in each of the tests failed to reveal the inactivation of sulfadiazine by any of the specimens.

2. Tests for sulfonamide-fastness of empyemal strains of pneumococcus.

Six strains from patients with empyema have been tested by *in vivo* methods, which consisted of infecting mice intraperitoneally and treating them with sulfadiazine, *per os*, twice daily for four days. Five of the strains came from the pleural exudate of patients who were treated at the onset of the pneumonia with sulfadiazine. With each of these strains some degree of drug resistance was evident in that an amount of sulfadiazine sufficient to cure mice infected with laboratory strains of pneumococci was incapable of preventing death in mice infected with empyemal strains.

The sixth strain, however, derived from a patient treated from the beginning with penicillin alone had no degree of drug fastness either to sulfadiazine or penicillin.

Although the findings just outlined are too limited to warrant final conclusions, they suggest that, in cases of pneumonia which develop empyema while receiving sulfonamide drugs, the strain derived from

the pleural exudate may exhibit sulfonamide-resistance. On the other hand, if no sulfonamide therapy has been administered, the empyemal strain may be found to be drug susceptible.

That penicillin warranted trial in this type of infection is indicated by the fact that its antibacterial action against pneumococci is equally potent irrespective of the presence or absence of sulfonamide-fast qualities.<sup>9, 12, 13</sup>

In attempting to develop an effective but uncomplicated method by which penicillin may be utilized locally in pneumococcal empyema, the patients receiving treatment have been studied by correlating their clinical course with the results of laboratory examinations of specimens of pleural exudate derived from the treated area.

The findings have been used as an indication of the degree of effectiveness of varying dosages of penicillin and also as a guide in determining the extent to which repeated injections were necessary.

#### MATERIAL AND METHODS

In pursuing the studies, samples of pleural effusion were obtained by bedside aspiration at frequent intervals and examined for the presence of viable pneumococci. When pus suspected of containing penicillin was cultured, the specimen was first centrifuged and washed with physiological salt solution in order to avoid transferring a portion of the antibacterial agent contained in the exudate to the broth used for culture media. It may be noted, however, that in comparable tests using 0.1 cc. of specially prepared exudate added to 5 cc. of broth, the preliminary washing did not yield results different from that obtained by adding the same amount of pus directly to the culture media. It seems unlikely that the special technique is necessary as a routine procedure in determining the presence or absence of viable organisms.

In some instances, tests for the presence of penicillin in the exudate were made in order to estimate the duration of its activity following instillation. The method most frequently employed consisted of determining the capacity of the supernatant fluid of centrifuged specimens of effusion to protect mice against infection with pneumococci heterologous in type to that derived from the patient. By this procedure, active penicillin was detected in the exudate for as long as 48 hours after injection in four patients and 72 hours in another patient but was not demonstrable in specimens obtained on the 5th or 6th day following

treatment. As will be discussed later, the duration of sterility has served as a supplementary guide in establishing the quantity and frequency of injections that comprised effective therapy.

*Concentration of Penicillin in Solution Used for Injection.* Solutions were most commonly made up in a concentration of 1000 units of penicillin in 1 to 1.5 cc. of physiological salt solution. The quantity of solution injected was never in excess of the amount of exudate removed. However, since the largest single dose injected intrapleurally was 40,000 units in 50 cc. and since the amount of exudate aspirated was usually more than 50 cc., the necessity of using a more concentrated solution in order to introduce the desired number of units did not frequently occur. In view of the moderate irritating effect of penicillin on the serous surface of the pleura as indicated in Table IV, the concentration may, under some circumstances, require consideration.

#### CLINICAL COURSE AND LABORATORY FINDINGS OF THE PATIENTS

The results derived from the study are given in the form of a brief resume of the course of each patient. Charts of four of the patients are included. X-ray photographs, taken before treatment was begun and after recovery, of 6 patients are appended at the end of this article.

*Case 1.* Patient A.Mc., male, white, age 57 years.

*Diagnosis:* Lobar pneumonia, bacteriemia, empyema, *Pneumococcus*, Type I.

The patient was admitted to our wards on the 21st day of illness. In the early stages of pneumonia he had been treated with sulfadiazine. The blood culture became sterile and pneumonia subsided following sulfadiazine therapy but signs of pleural effusion developed. On three separate occasions during the first two weeks of the patient's illness purulent material containing Type I pneumococci was obtained by thoracentesis. One week after the last of the preceding aspirations the patient came under our observation.

The patient's course is illustrated in Chart 3.

From Chart 3 it may be seen that the local treatment of empyema first consisted of 5 gms. of sulfadiazine injected intrapleurally. As mentioned earlier the failure of sulfadiazine to sterilize the cavity was accounted for by the drug-fastness of the infecting strain.

At the time of the first injection of penicillin 400 cc. of thick puru-



X-RAY PHOTOGRAPHS OF CASE 1.

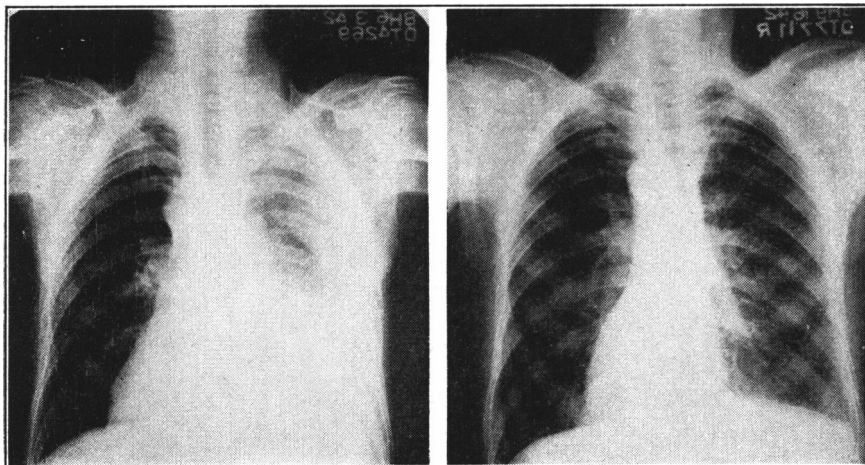


Fig. 1 Before penicillin therapy.

Fig. 2 Two months after leaving hospital.

only evidence of abnormality consisted of a small localized band of increased density in the left lateral costophrenic angle.

*Resume: Total Number of Intrapleural Injections of Penicillin: Two.*

*Amount per Dose: 40,000 units.*

*Total Amount: 80,000 units.*

*Result: Pleural exudate sterile 24 hours after first treatment. No relapses. Recovery complete with limited residual pleural thickening.*

*Duration of Hospitalization After Beginning of Treatment: 42 days.*

*Case 2. Patient E.M., male, colored, age 35 years.*

*Diagnosis: Lobar pneumonia, bacteriemia, empyema (multiple foci). Pneumococcus, Type VIII.*

The patient was treated for the first 10 days with sulfadiazine by mouth. Blood culture became sterile but high fever persisted. Empyema was detected on 6th hospital day. Sulfonamide-fastness of empyemal strain was demonstrated by laboratory tests.

The first intrapleural injection of penicillin (20,000 units) was given on the 10th hospital day. Three additional doses (15,000, 20,000, and 25,000 units respectively) were given into the same site as that of the first injection. The latter treatments were administered on the 2nd,

## X-RAY PHOTOGRAPHS OF CASE 2.

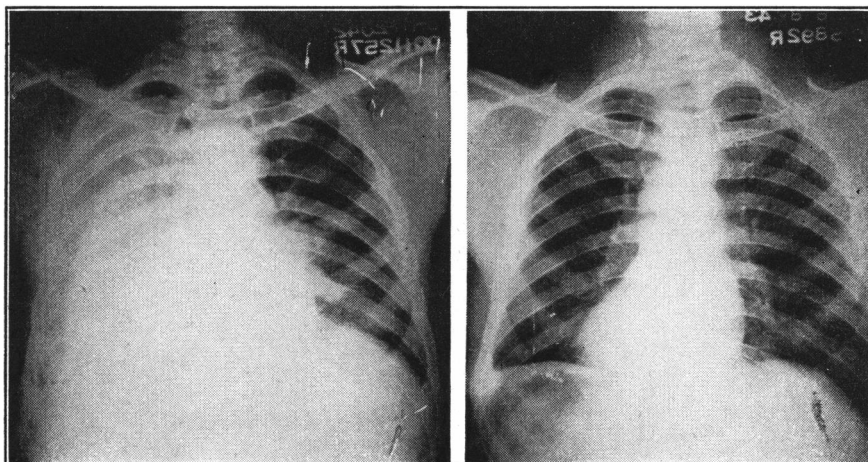


Fig. 3 Before penicillin therapy.

Fig. 4 Four months after leaving hospital.

4th, and 7th day after the initial instillation. Five samples of exudate were taken from the area subjected to repeated treatments between the 1st and 15th day after beginning injections and, in each instance, cultures were sterile.

In spite of the disappearance of pneumococci from the site of infection receiving the repeated injections, the patient continued to be acutely ill. By additional explorations, a second pocket of empyema was found, the exudate from which contained Type VIII pneumococci. Before penicillin therapy was instituted into the second area, the patient began to cough up large quantities of purulent material. The course was interpreted as indicating that the second pocket was being drained through a bronchopleural opening. After 2 weeks the sputum became scanty and ceased to be purulent. The patient was improved but not afebrile.

Subsequently his temperature rose to  $104.5^{\circ}$ . A third pocketed area was discovered distant from the other two. No viable pneumococci were recovered from the purulent fluid of this area but a precipitin test performed by mixing the specimen of exudate with Type VIII antipneumococcus serum was strongly positive.

Into the third area 20,000 units of penicillin were injected. Within 48 hours the patient's temperature was normal and his convalescence

to recovery was rapid. X-ray photographs are appended. The last picture was taken four months after discharge from hospital.

*Total Number of Intrapleural Injections of Penicillin:* Four into the first focus, one into the third focus.

*Amount per Dose:* 20,000—15,000—20,000—25,000 units into the first pocket; 20,000 units into the third pocket.

*Total Amount:* 100,000 units.

*Result:* Pleural exudate of first pocket sterile 24 hours after first treatment. No recurrence of infection in first area but additional pockets were present. Final recovery was complete with limited residual pleural thickening.

*Duration of Hospitalization:* 62 days after beginning treatment, 15 days after treatment of last localized area of infection.

*Case 3.* Patient M.B., white, male, age 33 years.

*Diagnosis:* *Lobar Pneumonia, Empyema. Pneumococcus, Type V.*

The patient was treated for the first five days with sulfadiazine by mouth. Empyema was detected on 2nd hospital day. Local penicillin therapy was instituted on the 3rd hospital day by injecting 40,000 units intrapleurally. No additional treatments were given.

The pleural exudate obtained from each of two pre-treatment taps contained Type V pneumococci. From five subsequent aspirations performed two, six, eight and fifteen days after instillation of penicillin, 200-300 cc. of cloudy material were obtained. No pneumococci were present.

His general condition progressed satisfactorily except for low grade fever which continued for 16 days, together with a moderate leukocytosis, and some night sweats. It is interesting to note that in spite of the inability to demonstrate bacteriologically active infection, the exudate in the pleural cavity continued to accumulate for approximately two weeks before finally disappearing.

*Resume: Total number of Intrapleural Injections of Penicillin:* One.

*Total Amount:* 40,000 units.

*Result:* Pleural exudate sterile 48 hours after local treatment. No relapses. Clinically recovery was complete, but patient was not under observation for a sufficient length of time to observe the final degree of clearing of x-ray shadow.

*Duration of Hospitalization after Beginning Treatment:* 25 days.



TABLE IV  
IRRITATING EFFECT OF PENICILLIN INJECTED INTRAPLEURALLY

Case No.	Diagnosis	Pleural Fluid W. B. C.	Penicillin Units	1st Day			2nd Day			4th Day			6th Day					
				Cells	Fever	Pain	Cells	Fever	Pain	Cells	Fever	Pain	Cells	Fever	Pain	Cells	Fever	
1	TBC	590	40,000	Not done			1820					560						
2	Cardiac	255	12,500	64,200	+	+	36,800	+	—	—	—	3200	—	—	—	—	—	310
3	Cardiac	320	10,000	17,500	+	+	13,500	+	—	—	—	2920	—	—	—	—	—	810
4	Cardiac	620	10,000	14,500	+	+	8900	—	—	—	—	2750	—	—	—	—	—	1680
5	Cardiac	180	5,000	15,500	+	+	2190	—	—	—	—	—	—	—	—	—	—	1000
6	Pneu.	210	5,000	2975	+	+						1225	+					
7	Alc. Cirv.	770	5,000		—	—	1150	—	—	—	—							250
8	Cardiac	1830	5,000	5,500	—	—												
9	Cardiac Same as 2	340	Control	520	—	—						540	—					

The special features of the cases so far described consisted of: 1. The rapidity of sterilization of the empyemal cavity following injection of penicillin; 2. The persistence or probable reaccumulation of purulent exudate without demonstrable pneumococci; 3. The somewhat prolonged convalescence with low grade fever; 4. The ultimate recovery.

In considering an explanation of the course, which was characterized in each of the patients by rapid bacteriological "cure" but somewhat delayed clinical resolution, the possibilities which suggested themselves were that a small focus of undetected living organisms remained under the fibrin coating of the pleura even though aspirated material was sterile, or that the decomposition of the sterile pus produced toxic substances acting as irritants, or that the penicillin was itself irritating locally.

The latter possibility lent itself readily to testing. Accordingly, solutions containing from 5,000 to 40,000 units were injected intrapleurally into eight patients who suffered from hydrothorax due to various causes. The penicillin was introduced after removal of most of the transudate. Subsequent samples of the effusion were obtained on each of the following four to six days and the number of cells per cmm. was determined. The presence or absence of fever or thoracic pain was also noted. The results are contained in Table IV.

In each instance there was a definite but variable rise in the number of cells which was greatest the day after injection and gradually decreased during the ensuing days until a number slightly above the pre-injection level was reached on the 4th to 6th day. Slight fever (100-101°) and some thoracic pain were present on the day following injection but disappeared within 48 hours.

In view of the evidence of a moderate irritating action of penicillin on the pleural surfaces, the next two patients received smaller doses of penicillin than those employed in the cases already described. The attempt was made to employ a sufficient number of units to obtain the necessary antibacterial effect but to minimize the untoward local reaction. That the dosage employed for that purpose was insufficient is evident from the relapses which occurred in the next two patients.

*Case 4.* Patient M.L., white, female, age 42 years.

*Diagnosis:* *Lobar pneumonia, Bacteriemia, Empyema. Pneumococcus, Type V.*

## X-RAY PHOTOGRAPHS OF CASE 4.

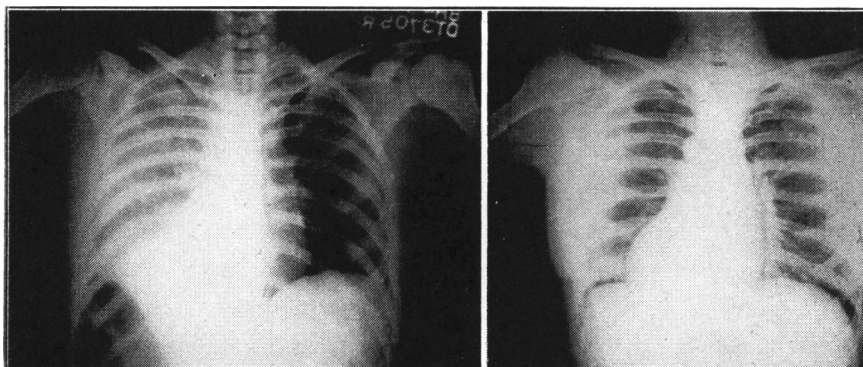


Fig. 5 Before penicillin therapy.

Fig. 6 Two months after leaving hospital.

On admission, treatment for the first three days consisted of penicillin given intravenously. A total of 130,000 units was administered. The bacteriemia cleared within 24 hours. Empyema was demonstrated on the 4th hospital day.

It is interesting to note that penicillin given during the early acute phase of the illness did not in this instance prevent the development of empyema.

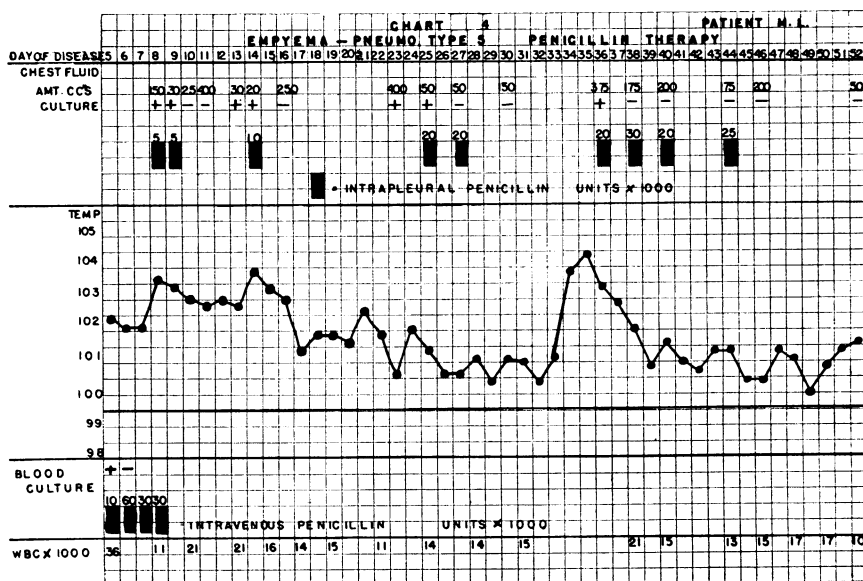
The difficulties in the course of the empyema in Case 4 which were referable to insufficient treatment are illustrated in Chart 4.

From Chart 4 it may be noted that following the injection of 5,000 units, the cavity was not sterilized but that after the second injection of an additional 5,000 units, two aspirations performed 24 and 48 hours later yielded material from which pneumococci were not obtained.

The patient, however, had three subsequent relapses as measured by a return of cultivable pneumococci to the pleural exudate. At each recurrence the dosage of penicillin was gradually increased. The infection was finally overcome by administering four separate doses on alternate days of 20,000-30,000 units.

In spite of her prolonged and irregular course due to inadequate treatment at the beginning, recovery occurred without any greater residue of pleural thickening than that seen in the other cases.

X-ray photographs are appended the last of which was taken two months after discharge from the hospital.



*Resume: Total Number of Intrapleural Injections of Penicillin: 9. Amount per Dose: As indicated in Chart 4 they varied from 5,000 to 30,000 units.*

*Total Amount: 155,000 units.*

*Result: Three recurrences of demonstrably viable pneumococci after transient periods of negative cultures. Ultimate recovery was complete with limited pleural thickening.*

*Duration of Hospitalization after Beginning Treatment: 79 days.*

*Case 5. Patient M.J., white, male, age 2 years, 3 months, admitted to Pediatric Service of Bellevue Hospital\* on 6th day of disease.*

*Diagnosis: Lobar Pneumonia, Empyema. Pneumococcus, Type XVI.*

The patient was treated with sulfathiazole and sulfadiazine for the first 12 days of hospitalization without notable improvement. The first successful thoracentesis yielding pus was performed in the 14th hospital day.

The treatment with penicillin in this patient was started by using small doses as in Case 4. The first injection consisted of 5,000 units.

\* The patient's record is presented with the permission of Dr. James Wilson, Director of the Pediatric Service.

## X-RAY PHOTOGRAPHS OF CASE 6.

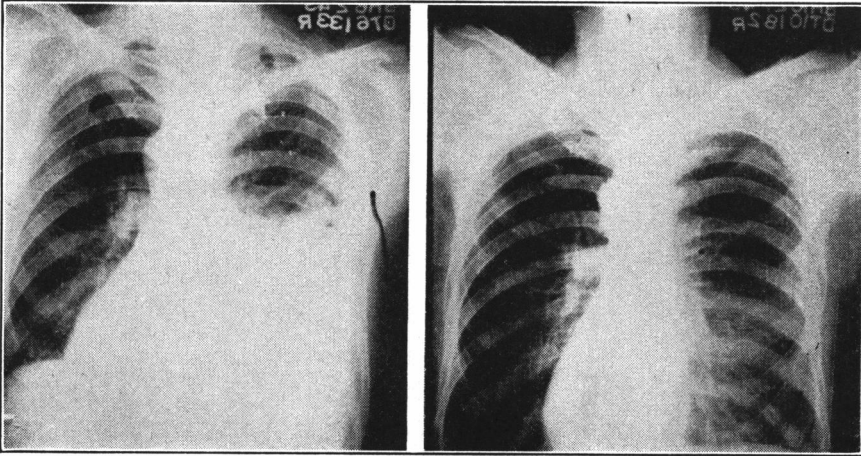


Fig. 7 Before penicillin therapy.

Fig. 8 Four months after leaving hospital.

Two aspirations done one and five days after treatment yielded exudates which were sterile on culture. Viable organisms returned, however, within six days. Additional intrapleural doses of 15,000 and 10,000 units were administered which afforded only transient suppression of cultivable organisms.

Following the second relapse surgical drainage was carried out by rib resection. The patient recovered after a prolonged postoperative convalescence.

*Resume: Total Number of Intrapleural Injections of Penicillin: 3.*

*Amount per Dose: 5,000—10,000—15,000 units.*

*Total Amount: 30,000 units.*

*Result: Penicillin therapy unsatisfactory due to insufficient dosage. Surgical drainage required. Recovery was complete.*

*Duration of Hospitalization: 131 days following thoracotomy.*

*Case 6. Patient, J.D., white, male, age 58 years.*

*Diagnosis: Lobar Pneumonia, Empyema, Pneumococcus, Type 1.*

The patient was treated with sulfadiazine by mouth for the first eight days of his illness. Empyema was diagnosed on the sixth hospital day. The empyemal strain was found to possess a definite degree of sulfonamide resistance. Following aspiration of the chest on the eighth

hospital day, 25,000 units of penicillin were instilled into the empyemal pocket.

Both of the pre-treatment specimens of pleural exudate were positive on culture for Type I pneumococci. Material aspirated on the day following treatment was sterile. Cultures of all subsequent samples were also negative.

The total amount of treatment given to the patient consisted of three injections of 25,000 units each injected on alternate days.

His clinical course, similar to that of the other patients who did not suffer relapse, was characterized by gradual improvement, but he maintained a slight fever of 99.5 to 100.5° until the 47th hospital day. The delayed absorption of the thick though sterile exudate was particularly striking.

In considering the possibility that the protracted low grade illness might be caused by active undetected infection, intensive therapy was carried out for six days. During the first three days 140,000 units of penicillin were given intravenously and 30,000 units were injected on two occasions intrapleurally. During the remaining three days 20 gms. of sulfadiazine were administered by mouth. No appreciable response occurred.

As an additional measure, when no signs of gradual absorption of the residual exudate could be detected, the site of the pleural pocket was irrigated with physiological salt solution in order to remove as much as possible of the degenerated abacterial pus. Following three irrigations on alternate days the presence of exudate was no longer demonstrable. No effusion reformed and progress to recovery was uneventful.

*Resume: Total Number of Intrapleural Injections of Penicillin: 3.*

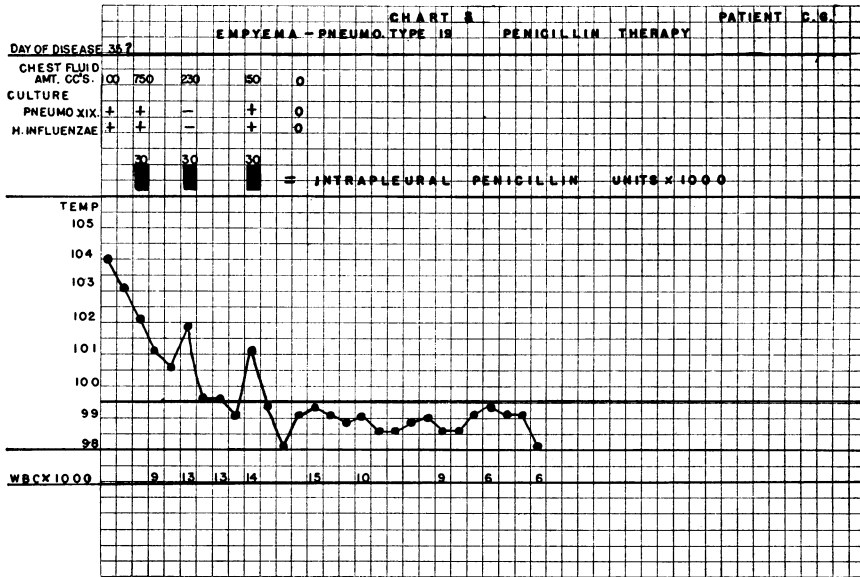
*Amount per Dose: 25,000 units.*

*Total Amount: 75,000 units.*

(The amounts given above do not include the late period of additional therapy since the latter treatment did not influence the abacterial pus.)

*Result: Pleural exudate sterile 24 hours after first treatment. No relapses. Recovery was complete with residual thickening of pleura.*

*Duration of Hospitalization after Beginning Treatment: 51 days.*



Case 7. Patient C.G., white, female, age 27 years.

*Diagnosis: Pneumonia, Pneumopyothorax. Pneumococcus, Type XIX, Hemophilus Influenzae.*

The patient had been ill six weeks before admission with a disease which began as an upper respiratory infection. Her local physician had tapped her chest on one occasion and obtained fluid. When her condition remained unchanged she was admitted to the hospital suspected of having tuberculosis. Her course is illustrated in Chart 5.

On admission x-ray examination revealed the presence of both an effusion and air in the right pleural cavity; 100 cc. of thick purulent exudate were removed by thoracentesis. Pneumococcus, Type XIX and Hemophilus influenzae were both seen and cultured from the pus.

Following a second aspiration performed two days later, 30,000 units of penicillin were introduced after removal of 750 cc. of infected exudate.

Cultures of material obtained three days later yielded no growth. The suppression of H. influenzae is of interest since Fleming<sup>4</sup> did not find the strains of H. influenzae which he tested to be susceptible to the antibacterial action of penicillin. It seems likely that the concentration of penicillin introduced into the pleural cavity may have accounted for

X-RAY PHOTOGRAPHS OF CASE 7.

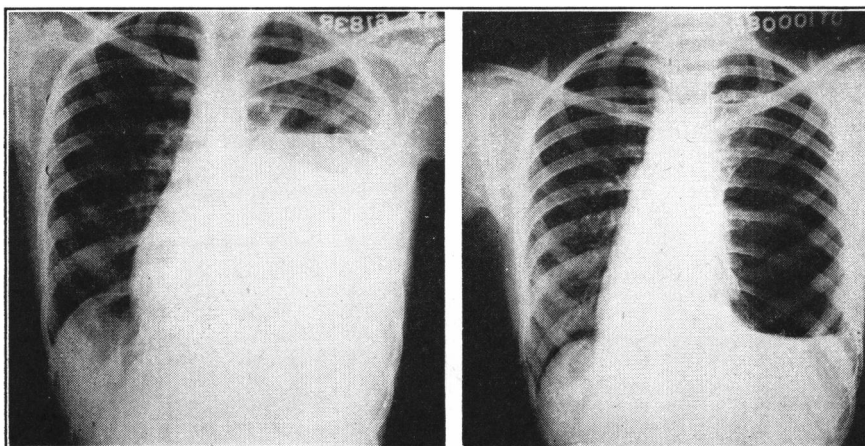


Fig. 9 Before penicillin therapy.

Fig. 10 Two months after leaving hospital.

the effect or that the patient's strain was unusually susceptible to penicillin.

Four days after the second intrapleural treatment, pneumococci and *H. influenzae* were again seen in smears and cultivated from an aspirated sample of exudate. However, after the third instillation of 30,000 units subsequent efforts to obtain fluid were unsuccessful. The patient rapidly improved, her temperature becoming normal 18 days after beginning treatment.

The unusual feature of the course of this patient was the persistence and even increase in the pneumothorax in spite of the rapid disappearance of the pyothorax. Her general clinical improvement paralleled her temperature course as presented in Chart 5. Up to the present time, four months after discharge from the hospital, no signs of effusion have developed in the affected side, but the bronchopleural fistula remains unhealed.

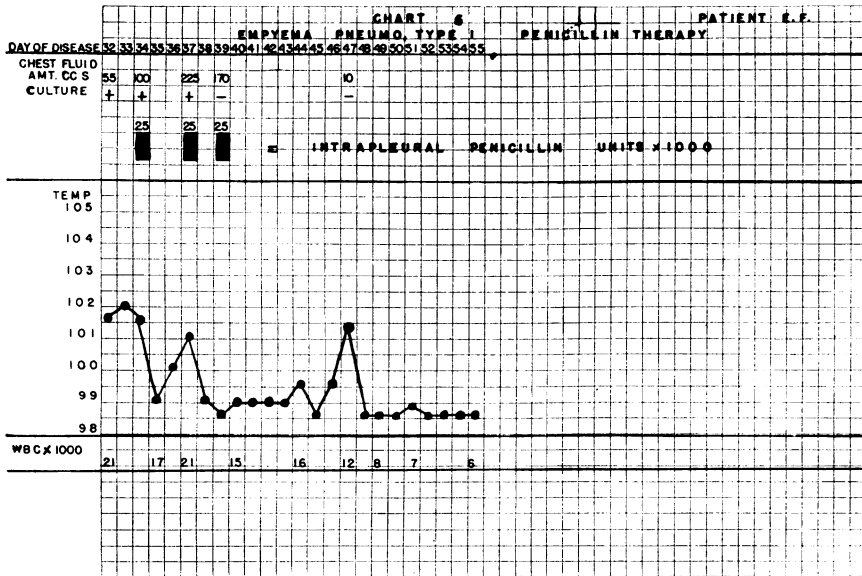
*Resume: Total Number of Intrapleural Injections of Penicillin: 3*

*Amount per Dose: 30,000 units.*

*Total Amount: 90,000 units.*

*Result: One bacteriological relapse following second treatment. The pyothorax together with clinical and laboratory signs of infection disappeared but pneumothorax persisted.*





*Duration of Hospitalization Following Beginning of Treatment: 26 days.*

*Case 8. Patient E.F.,\* colored, female, age 11 years.*

*Diagnosis: Lobar Pneumonia, Empyema. Pneumococcus, Type I.*

The patient, treated on the Pediatric Service, received sulfadiazine for the first few days but continued to be ill. Suggestive signs of pleural effusion developed but pus was not obtained until 25 days after admission. Type I pneumococci were present in the exudate.

The course of the illness is represented in Chart 6.

The patient received 25,000 units of penicillin on three occasions, spaced three and two days apart respectively. Cultures of the exudate were sterile after the second treatment. The clinical improvement was rapid, her temperature becoming normal five days after receiving the initial injection of penicillin.

*Resume: Number of Intrapleural Injections of Penicillin: 3.*

*Amount per Dose: 25,000 units.*

*Total Amount: 75,000 units.*

*Result: Pleural exudate sterile five days after beginning treatment. No relapses.*

\* See Page 156.

## X-RAY PHOTOGRAPHS OF CASE 8.

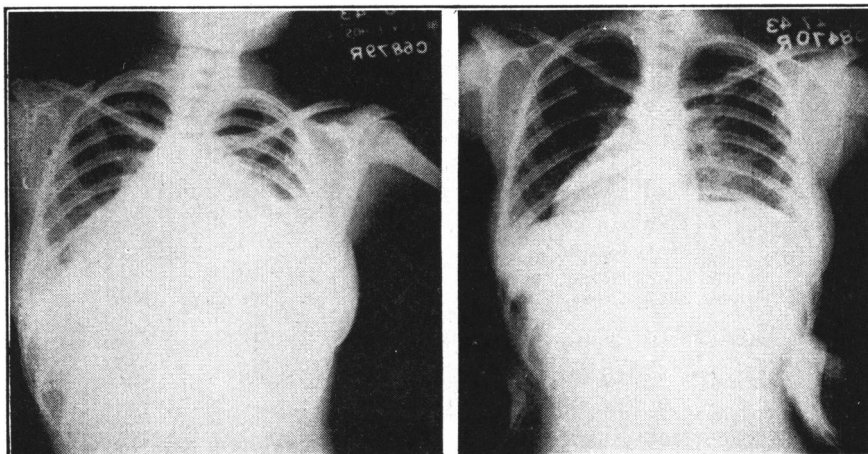


Fig. 11 Before penicillin therapy.

Fig. 12 One week after leaving hospital.

Recovery was complete.

*Duration of Hospitalization After Beginning Treatment:* 21 days.

## DISCUSSION AND OUTLINE OF TREATMENT

It is evident from the results which have been described that penicillin injected locally into the pleural cavity is capable under proper circumstances of effecting a cure in pneumococcal empyema without requiring surgical drainage. In developing the most suitable procedure for administering the drug consideration has been given to the therapeutic requirements with respect to amount of penicillin per dose, the frequency with which the injections should be repeated, and the number of repetitions that may be necessary. Although no arbitrary standards may be set at the present time, the favorable results so far obtained constitute a basis for formulating the details of treatment.

*Amount of Penicillin, per dose, for Intrapleural Injection.* In the two cases which received 5,000 to 10,000 units, pneumococci disappeared temporarily from the pleural exudate as determined by microscopic examination and culture of the specimens but relapses occurred in both instances.

When larger doses ranging from 25,000 to 40,000 units were employed, in only one instance did a relapse occur (Case 7), and even in

that case the infection was subsequently eliminated following one additional dose.

On the basis of present experience, therefore, 30,000 to 40,000 units appears to be an adequate amount per dose.

*Frequency of Injections.* The preliminary studies mentioned earlier in this article indicated that the activity of penicillin is retained for at least 48 hours to 72 hours after injection into an empyemal pocket. The fibrinous exudate appears to retard absorption but does not destroy the antibacterial quality at a rapid rate.

Furthermore, the tests carried out with repeated samples of exudate have shown that the initial suppression of the organisms that follows treatment is maintained for at least two to three days.

On the basis of these findings, therefore, no demonstrable advantage seems to be gained by performing thoracentesis oftener than every other day.

*Number of Repeated Injections.* Even though Case 2 recovered following a single injection of 40,000 units, and Case 1 received only two injections of 40,000 units each, treatment in the other patients was extended to at least three separate injections. In view of the fact that the end point of active infection is liable to be obscured by the persistence of low grade fever and the delayed absorption of the exudate even though sterile, the determination of the time at which treatment may be stopped has not been clearly defined. On the basis of practical experience, however, when clinical improvement appears to be progressive and the exudate remains sterile, three separate injections may, in most instances, be sufficient.

#### PLAN OF TREATMENT

Thirty to forty thousand units of penicillin contained in 30 to 50 cc. of isotonic salt solution injected intrapleurally on alternate days for at least three doses.

As a further measure in hastening recovery it is desirable at the time of bedside aspiration to irrigate the cavity with a few hundred cc. of physiological salt solution before introducing the penicillin and to repeat the procedure, if necessary, at intervals of several days after treatment is stopped in order to hasten the removal of the degenerated sterile exudate and minimize the reaccumulation of an effusion.

SUMMARY

I. *Lobar Pneumonia*. Penicillin has been found to be highly effective in the treatment of pneumococcal pneumonia.

Of 46 treated patients, 3 (6.5 per cent) died and 39 recovered in a striking manner indicating the special value of the drug. The response was not clearly defined in 4 patients, one of whom probably had primary atypical pneumonia and the other 3 had unrelated underlying pulmonary diseases which prolonged their illness beyond the usual course of pneumonic resolution.

Bacteriemia, which occurred in 14 of the patients, disappeared in every instance following injections of penicillin.

On the basis of quantitative data presented and discussed in this article, a tentative regime for the treatment of pneumonia with penicillin is outlined.

Factors relating to the relative values of penicillin and sulfadiazine in the treatment of pneumonia are discussed.

II. *Pneumococcal Empyema*. Eight patients with pneumococcal empyema have been treated by intrapleural injections of penicillin.

In seven, the infection was eliminated by the local therapy without requiring surgical drainage. Six of them recovered completely with only a restricted area of pleural thickening remaining as a permanent alteration.

In one patient, who had pyopneumothorax on admission, the pyothorax cleared up satisfactorily but the pneumothorax arising from a bronchopleural fistula which was present before treatment was begun, has persisted.

In another patient, who was insufficiently treated at the beginning with penicillin, relapse occurred and surgical drainage was instituted.

Following discharge from the hospital, the patients have returned for reexamination at varying periods, after one week for one patient, and from 4 to 6 months for the others. With the exception of the case with pneumothorax, the others have remained well and free of symptoms.

Strains of pneumococci derived from the empyemal pus of patients whose pneumonia had been previously treated with sulfadiazine were found to possess varying but definite degrees of sulfonamide-resistance.

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