

A FURTHER STUDY OF ETHYLHYDROCUPREIN (OPTO- CHIN) IN THE TREATMENT OF ACUTE LOBAR PNEUMONIA *

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In a previous communication¹ we reported on a series of thirty-two cases of lobar pneumonia due to pneumococci and treated with ethylhydrocuprein (optochin) hydrochlorid. By means of bactericidal tests of the patient's serum in vitro the absorption and elimination of the drug in these cases was studied. It was concluded that the hydrochlorid of the drug is rapidly absorbed from the gastro-intestinal tract into the circulating blood; that when an amount of the hydrochlorid represented by 0.024 to 0.026 gm. per kilogram of body weight of the patient is administered by mouth per twenty-four hours, the blood serum of the patient acquires the property of destroying pneumococci in the test tube; that the best way to insure the rapid production and maintenance of this bactericidal action in the blood is to divide the total amount of the drug in such a way that the first dose is relatively large and is followed at intervals of not more than three hours by smaller equal doses. For example, if the patient is of average size and is to receive 1.5 gm. in twenty-four hours, he is given a first dose of 0.45 gm., and this is followed by seven doses of 0.15 gm. each at regular intervals. It was further shown that during administration of the drug the pneumococci in the body may become "fast" or resistant to a considerable concentration of ethylhydrocuprein.

The purpose of the present paper is to present the data accumulated in an extension of the former work and to give the final results of two years' experience in the treatment of lobar pneumonia with ethylhydrocuprein. It may be stated that the experimental results obtained during the first year have been for the most part confirmed by the study of cases treated during the second year, and, in addition, some new facts have been ascertained which it is desirable to record. The experimental observations will be recorded first, and then the entire series of cases will be analyzed from a clinical standpoint.

The method of investigation described in the previous paper has

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1. Moore, H. F., and Chesney, A. M.: THE ARCHIVES INT. MED., 1917, **19**, 611.

again been used and has been found satisfactory. Briefly, this consisted in repeated determinations of the bactericidal power of the patient's serum at 37.5 C. for young (four to six hours) broth cultures of pneumococci. The strains used were stock strains and usually the type of pneumococcus employed for any case differed from that causing the infection. Almost all the patients admitted to the wards of the Hospital of The Rockefeller Institute from October, 1915, to May, 1917, suffering from lobar pneumonia due to pneumococci belonging to Groups II, III and IV, were treated with ethylhydrocuprein. Cases due to pneumococci of Group I did not receive ethylhydrocuprein, but were treated with specific immune serum. A limited number of patients infected with pneumococci of Groups II and III were treated with ethylhydrocuprein by mouth and in addition received type homologous immune serum intravenously, or concentrated "extract" of such serum subcutaneously or intravenously.

Of the forty-three patients treated with ethylhydrocuprein during the season 1916-1917, two received the base (optochin base) by mouth. Forty received the hydrochlorid by mouth and one patient received the hydrochlorid intramuscularly at first, and later by mouth. In Table 8 are presented the details as to dosage of the drug, clinical features and so forth, in these forty-three cases.

ADMINISTRATION OF ETHYLHYDROCUPREIN BASE BY MOUTH

The serum of the patients (Nos. 2786 and 2783) who received the base by mouth failed to show either bactericidal activity or power temporarily to inhibit the growth of pneumococci, although the amount of the drug given should have been sufficient to produce such a result if the base were as readily absorbable as the hydrochlorid. The difficulty of absorption from the gastro-intestinal tract is undoubtedly dependent on the fact that the drug in this form is very slightly soluble.

"FASTNESS" OF PNEUMOCOCCI TO ETHYLHYDROCUPREIN

In our former communication we reported one instance in which the infecting pneumococcus became "fast" to ethylhydrocuprein in the human body. A further example of this phenomenon has been observed in the present study. The details follow:

Hosp. No. 2825.—A street cleaner, aged 50; weight 69 kg.

Past History.—Unimportant.

Present Illness.—Cough for one day; chill and bloody expectoration on day of admission.

Status on Admission.—Patient dyspneic, cyanotic and decidedly ill; temperature 105.2 F.; pulse 120; respirations 32; dulness with suppression of breath sounds and numerous fine moist râles over left lower lobe. Leukocyte count 15,000. Sputum tenacious, hemorrhagic and containing *Pneumococcus* Type II. Blood culture showed *Pneumococcus* Type II, three colonies per cubic centimeter.

Course and Treatment.—Ethylhydrocuprein hydrochlorid started by mouth on second day of disease; schedule as follows in periods of twenty-four hours: first period, 1×0.6 gm. + 8×0.15 gm. (0.026 gm. per kilo of body weight per twenty-four hours); second period, 12×0.15 gm.; third period, 11×0.15 gm.; last period of eighteen hours, 7×0.15 gm. + 2×0.1 gm. Blood culture taken thirty-six hours after the commencement of the ethylhydrocuprein treatment showed twenty-four colonies of pneumococcus Type II per cubic centimeter of blood and the patient's general condition seemed worse at that time. On the following day the blood culture showed sixty colonies per cubic centimeter and on the last day of life blood culture showed 700 colonies of *Pneumococcus* Type II per cubic centimeter of blood. The patient became progressively worse and died on the fifth day after admission to the hospital. Judging from physical signs, spread of the infected area in the lungs did not take place. The total amount of ethylhydrocuprein given was 6.5 gm. No toxic symptoms referable to the drug were observed.

Samples of blood serum of this case were obtained before beginning treatment and eight times during the course of treatment; these samples were tested for pneumococidal power against a four-hour-old culture of *Pneumococcus* Type II. *Pneumococci* grew unhindered in the specimen obtained before beginning treatment, but the tests of the specimens obtained later showed that the ethylhydrocuprein conferred the usual degree of pneumococidal power on the serum as early as 5.5 hours after the first dose was administered and that this pneumococidal power was maintained throughout the treatment.

The specimens of patient's serum showing pneumococidal power were pooled and the effect of the pooled serum on two strains of pneumococci, obtained from the patient's blood, was studied; one of these strains was obtained from the patient's blood on admission to the hospital and before the ethylhydrocuprein treatment was started and the other strain from his blood two hours before death. The results are given in Table 1. The technic employed was that previously described,¹ using 0.001 c.c. of a four-hour-old broth culture to inoculate 3 c.c. of serum. The serum was previously heated at 56 C. for one half hour. The bacterial count of the plates is given in approximate figures.

TABLE 1.—RESULTS OF ETHYLHYDROCUPREIN INJECTIONS IN HOSPITAL No. 2825

Serum	Strains of <i>Pneumococcus</i> Obtained from Blood	Number of Colonies of <i>Pneumococci</i> per 0.5 C.c. of Serum When Plated*		
		Immediately	After 1½ Hours Incubation	After 24 Hours Incubation
Before ethylhydrocuprein was started	On admission (before ethylhydrocuprein)	400	2,000	Confluent
	Two hours before death	400	2,000	Confluent
Pooled specimens obtained during ethylhydrocuprein treatment	On admission (before ethylhydrocuprein)	400	300	0
	Two hours before death	400	2,000	Confluent

* Approximate counts.

From Table 1 it is seen that whereas the strain obtained from the patient's blood before the ethylhydrocuprein treatment was started was readily killed by the pooled serum obtained during the administration of the drug, the strain obtained from the blood towards the end

of the treatment and shortly before the death of the patient was completely insusceptible to any pneumococcidal action of the same serum.

The effect of various concentrations of ethylhydrocuprein hydrochlorid in broth on the growth of the different strains of pneumococci obtained from this patient was also studied. In each test 0.1 c.c. of an eighteen-hour broth culture of the given strain was inoculated into 5 c.c. of the broth containing the ethylhydrocuprein, mixed and incubated for forty-eight hours. The degree of growth, if any, was judged macroscopically. Plates were also poured and smears examined after incubation.

TABLE 2.—GROWTH IN BROTH CONTAINING VARIOUS DILUTIONS OF ETHYLHYDROCUPREIN HYDROCHLORID OF STRAINS OF PNEUMOCOCCUS ISOLATED FROM BLOOD OF HOSPITAL No. 2825

Designation of Strain	Isolated	Number of Colonies in 0.000001 C.c. of Culture Used in Tests
A	From blood on admission.....	85
B	From blood on second day of ethylhydrocuprein treatment.....	101
C	From blood on third day of ethylhydrocuprein treatment.....	162
D	From blood on fourth day of ethylhydrocuprein treatment (2 hrs. before death)	150

Tube*	Dilution of Ethylhydrocuprein in Broth	Strain			
		A	B	C	D
1	1: 100,000	0	0	0	0
2	1: 200,000	0	0	0	0
3	1: 400,000	0	0	0	0
4	1: 600,000	0	0	0	Growth
5	1: 800,000	0	0	0	Growth
6	1:1,000,000	0	0	Growth	Growth
7	1:1,200,000	0	Growth	0	Growth
Control broth without ethylhydrocuprein.....		Growth	Growth	Growth	Growth

* Tubes incubated forty-eight hours at 37.5 C.

The results given in Tables 1 and 2 show definitely that during the course of treatment in this case the pneumococci in the body become gradually resistant to the action of the ethylhydrocuprein. The observations made in this case, together with the similar one made by us previously, not only demonstrate that this phenomenon of bacterial "fastness" may occur, but indicate that its occurrence is not infrequent.

BACTERICIDAL ACTION OF PERICARDIAL FLUID

We have previously reported¹ that a pericardial exudate obtained post mortem from a patient who had received ethylhydrocuprein hydrochlorid by mouth for several days possessed bactericidal properties. In the present series of cases the same phenomenon was demonstrated in pericardial fluids obtained post mortem from four other cases (Nos. 2800, 2849, 2919 and 3031). In each case the pericardial fluid was allowed to clot and the supernatant fluid was then pipetted off and used for bactericidal tests. Details of the tests of the pericardial fluid of two of these cases follow (Tables 3 and 4).

TABLE 3.—TEST OF BACTERICIDAL POWER OF BLOOD SERUM AND PERICARDIAL FLUID FROM HOSPITAL No. 2800

Tube Number	Blood Serum Obtained*	Number of Colonies of Pneumococci per 0.5 C.c. When Plated†		
		Immediately	After 1½ Hours Incubation	After 19¼ Hours Incubation
1	Before ethylhydrocuprein.....	501	2,960	Confluent
2	12 hours after first dose.....	268	54	0
3	35 hours after first dose.....	421	121	0
4	Pericardial fluid obtained post mortem*	301	345	1

* The pericardial fluid contained many pneumococci and it and the serum were heated at 56 C. for three-fourths hour before testing to destroy the contained pneumococci.

† Inoculation: 0.001 c.c. of a four-hour broth culture of *Pneumococcus* Type II.

TABLE 4.—TEST OF BACTERICIDAL POWER OF BLOOD SERUM AND PERICARDIAL FLUID FROM HOSPITAL No. 2919

Tube Number	Blood Serum Obtained	Number of Colonies of Pneumococci per 0.5 C.c. When Plated*		
		Immediately	After 1½ Hours Incubation	After 24 Hours Incubation
1	Before ethylhydrocuprein.....	1,200	2,400	Confluent
2	13 hours after first dose.....	1,200	Complete inhibition†	0
3	24 hours after first dose.....	800	Complete inhibition	84
4	69 hours after first dose.....	1,200	Complete inhibition	0
5	97 hours after first dose.....	1,000	Complete inhibition	0
6	Pericardial fluid obtained post mortem..	2,000	26

* Inoculation: 0.001 c.c. of a four-hour broth culture of *Pneumococcus* Type I.

† By complete inhibition of growth is meant no increase in the number of colonies.

In Hosp. No. 2849 the pericardial fluid obtained post mortem showed pneumococcidal action, although the blood serum obtained during the ethylhydrocuprein treatment showed only temporary inhibition of growth.

These observations show that when ethylhydrocuprein hydrochlorid is given by mouth according to the system of dosage used by us, it may pass into a serous sac (pericardial fluid) in amounts sufficient to exert a pneumococcidal action.

TOXIC DISTURBANCES OF VISION

In one of the patients of our former series¹ the administration of ethylhydrocuprein hydrochlorid led to the production of alarming and severe retinitis, from which, however, the patient recovered. In the present series eight patients complained of amblyopia, mild in three cases, more severe in five. On discontinuing the ethylhydrocuprein, vision was restored in all those who survived the pneumonia, and in the two who died the vision was improved after the discontinuance of the drug. Some details of these eight cases follow:

Hosp. No. 2940.—Housewife, aged 31; weight 74.2 kg.

Past History.—Unimportant.

Present Illness.—Chill, fever and pain in chest six days before admission.

Status on Admission.—Temperature 104.2 F.; pulse 136; respirations 44. Consolidation of left upper lobe; leukocyte count 41,400. Sputum tenacious, gray and contained *Pneumococcus* Type IV. Patient quite ill. Blood culture positive (four colonies per cubic centimeter).

Course and Treatment.—Ethylhydrocuprein hydrochlorid was started by mouth on the day of admission (seventh day of the disease) on a basis of 0.0269 gm. per kilogram of body weight for the first twenty-four hours (1×0.5 gm. + 10×0.15 gm.). During the second twenty-four hours 0.15 gm. was given every two hours. One hour after the second of these latter doses the patient complained of slight blurring of vision; later the vision seemed normal and the hearing became slightly impaired; about the time of the seventh dose (second twenty-four hours) the patient complained of "waves" before her eyes and continuous ringing in the ears and one and one half hours after this dose she complained that everything was "blurred and indistinct." The ethylhydrocuprein was therefore discontinued and after about eight hours the patient was seen by Dr. W. W. Weeks. His report on her visual condition stated that both disks were pale, that there were numerous small areas of edema scattered throughout the fundi, and that the patient could at this time count fingers at a distance of 6 feet. The patient died two days after the ethylhydrocuprein was stopped. The total amount of ethylhydrocuprein given was 3.05 gm.

The bactericidal test of the serum of this case showed that pneumococcidal action for a stock strain of *Pneumococcus* Type II was present in the serum ten hours after the administration of the first dose of ethylhydrocuprein (plate poured immediately after inoculation showed 800 colonies; plate poured after one and one-half hours incubation, 400; and plate poured after twenty-four hours incubation was sterile). Pneumococcidal action was also present in serum obtained twenty-three hours after the initial dose. The pneumococcidal action was no longer present in serum obtained shortly before death (ethylhydrocuprein having been discontinued for two days).

Hosp. No. 2885.—Woman, cook, aged 42; weight 49 kg.

Past History.—Unimportant.

Present Illness.—Headache, pain in chest and vomiting two days before admission, followed next day by chill; little cough or expectoration.

Status on Admission.—Temperature 102.8 C.; pulse 96; respirations 32. Involvement of right upper lobe posteriorly; leukocyte count 28,000; sputum slightly tenacious, not hemorrhagic, contained *Pneumococcus* Type II.

Course and Treatment.—Ethylhydrocuprein hydrochlorid was started by mouth on the day following admission, on a basis of 0.03 gm. per kilogram of body weight for the first twenty-four hours (1×0.45 gm. + 7×0.15 gm.); thereafter 0.15 gm. every three hours. After a total amount of 1.95 gm. had been given, the patient complained that she could not see; the administration of ethylhydrocuprein was thereupon discontinued. The pupils at this time were not dilated. About one hour later the patient could distinguish the outline of persons. Examination of the eyegrounds revealed no marked abnormalities. On the following day the vision was much improved and the eyes were examined by Dr. W. W. Weeks, who reported that there was indistinctness of both disk margins, the fundi were pale, the veins were somewhat dilated and tortuous, the arteries were of normal size, the vision was 20/20 in both eyes, and the fields were normal. About this time the patient could distinguish colors and said she could see quite well. This patient received, in addition to the ethylhydrocuprein, 770 c.c. of antipneumococcus serum, Type II, intravenously, in divided doses. The temperature reached normal on the eighth day of the disease. Pneumococcal power for a stock strain of *Pneumococcus* Type I was present in the serum of this case within twelve hours after the initial dose of ethylhydrocuprein.

Hosp. No. 2870.—Housewife, aged 46; weight 56.9 kg.

Past History.—Two previous attacks of pneumonia.

Present Illness.—Three days before admission, chill, nausea, pain in chest, cough, blood-tinged sputum.

Status on Admission.—Consolidation of left lower lobe; well marked friction rub over entire precordial region; area of cardiac dulness not enlarged. Temperature 105.1; pulse 112; respirations 34. Sputum bright, rusty-red, mucopurulent and contained *Pneumococcus* Type II.

Course and Treatment.—Ethylhydrocuprein hydrochlorid was started by mouth the day after admission (fourth day of disease) on a basis of 0.0263 gm. per kilogram of body weight per twenty-four hours (1×0.45 gm. + 7×0.15 gm.; thereafter 0.15 gm. every two and a half hours). On the second day of treatment with ethylhydrocuprein the patient seemed slightly deaf and after 2.7 gm. of ethylhydrocuprein had been given, on being questioned, the patient said that she could not see. The pupils were widely dilated. The ethylhydrocuprein was thereupon discontinued. Three and a half hours later she said her sight was better, and in six hours after the last dose of ethylhydrocuprein she could distinguish objects. The next day her sight was considerably better and the pupils less dilated. The patient was seen by Dr. W. W. Weeks a few hours after the ethylhydrocuprein treatment had been discontinued. Dr. Weeks reported as follows: "Fingers can be seen 1 foot distant; visual fields moderately contracted; color not recognized; media clear; disks and fundi pale; veins engorged; arteries somewhat narrow." Dr. Weeks' report two days later was as follows: "vision 20/40 + with both eyes; visual fields contracted, especially on nasal side; red or green cannot be distinguished; disks pale, especially on temporal side; fundi not pale; condition of vessels same as on previous examination." Her vision gradually improved and was normal when she left the hospital. Pneumococcal power for a stock strain of *Pneumococcus* Type I appeared in the blood serum of this patient within twenty-four hours of the administration of the first dose of ethylhydrocuprein.

Hosp. No. 2812.—Woman, aged 74; weight 58.5 kg.

Past History.—Unimportant.

Present Illness.—The patient said that she had not felt well for several days before admission. On the morning of the day before admission she felt very ill and had a temperature of 105 C., cough, blood-tinged sputum and pain in chest.

Status on Admission.—Temperature 104.1 F.; pulse 94; respirations 40. Involvement of the left lower lobe; emphysema present; sputum tenacious, rusty and yielded on passage through a mouse, *Pneumococcus mucosus* (Type III).

Course and Treatment.—Ethylhydrocuprein hydrochlorid was started by mouth on the day of admission, on a basis of 0.03 gm. per kilogram of body weight per twenty-four hours (1×0.6 gm. + 8×0.15 gm.; thereafter 0.15 gm. every two hours). After 0.9 gm. of the ethylhydrocuprein had been given the patient complained of hearing roaring noises, and after 3 gm. of ethylhydrocuprein she complained that she could not see. The ethylhydrocuprein was then discontinued. In six hours, however, she was able to count fingers and the next day her eyesight was much improved. Eight hours after the patient complained of loss of vision she was seen by Dr. W. W. Weeks, who reported that there was little change in the eyegrounds. The patient died on the fifth day after admission to the hospital.

Pneumococcal action for a stock strain of *Pneumococcus* Type II appeared in this patient's serum six hours after the initial dose of ethylhydrocuprein.

Hosp. No. 3015.—Engineer, aged 47; weight 75.8 kg.

Past History.—Unimportant.

Present Illness.—Chill, vomiting, headache, and pain in chest thirty-six hours before admission.

Status on Admission.—Temperature 104.6 F.; pulse 128; respirations 34. Consolidation of left lower lobe. Sputum obtained on admission was tenacious, frothy, rusty and contained *Pneumococcus mucosus* (Type III). Urine gave a definite precipitin reaction with antipneumococcus serum Type III.

Course and Treatment.—Ethylhydrocuprein hydrochlorid was started by mouth eleven and one-third hours after admission to the hospital on a basis of 0.034 gm. per kilogram of body weight per twenty-four hours (1×0.6 gm. + 10×0.2 gm.). After 2.4 gm. had been given the patient complained that he could not see distinctly and the ethylhydrocuprein was discontinued. At that time he could not see objects $1\frac{1}{2}$ feet from his eyes, but could distinguish direct light from darkness; the pupils were somewhat dilated and did not react to light; the veins were engorged and the eyegrounds somewhat pale. He had been questioned two and three-quarters hours previously as to whether he could see well, and replied that his vision was as good as normal; at that time he was partially deaf. Twelve hours after the complaint that vision was impaired, the patient could read a watch at 2 feet and a ward clock at about 20 feet, and said he could see well, but that objects were a little blurred. Later that day he was examined by Dr. W. W. Weeks, whose report is abstracted as follows: "Vision 20/40 + in both eyes; arteries injected; veins tortuous and engorged; left disk distinctly pale, especially the temporal half; visual fields restricted in both eyes, 10 degrees in right, and 20 degrees in left; color is recognized by left eye but not by right." Three days later Dr. Weeks reported as follows: "Pupils equal, contracted, reacted readily to light during accommodation and on convergence; vision without correction: O. D. 20/40 +, O. S. 20/210 with +1.25 O. D. 20/20, with +1.50 O. S. 20/20; concentric contraction for form, more in left eye; media clear; retina somewhat hazy near disks, so as to make disk margin a little indistinct; vessels normal except arteries of left eye which were somewhat smaller and more tortuous than those of right."

The temperature reached normal on the night of the day following admission to the hospital, but rose again thirty-six hours afterward and remained elevated for four days, although the pulse and respiration rates did not increase and the patient felt quite comfortable. The patient recovered.

The test of blood serum in this case showed pneumococcal action for a stock strain of *Pneumococcus* Type II.

Hosp. No. 2972.—Man; complained of slight transient blurring of vision at times after the temperature had become normal; ethylhydrocuprein was discontinued (see Table 8 for details of the case).

Hosp. No. 2837.—Man; complained of transient deafness; transient dimness of vision occurred after the temperature had become normal; ethylhydrocuprein was discontinued (see details of case in Table 8); the patient had an abrasion of the cornea and there was some inflammation of the right cornea on the morning that he complained of dimness of vision.

Hosp. No. 2911.—Woman; complained of dimness of vision and slight partial deafness after she had received 2.95 gm. of ethylhydrocuprein hydrochlorid by mouth; both passed off after ethylhydrocuprein had been discontinued (for details of the case see Table 8).

In our entire series of seventy-five cases, nine, or 12 per cent. of the patients, showed some degree of amblyopia. Of all the patients treated with ethylhydrocuprein which are recorded in the literature, between 4 and 5 per cent. suffered from amblyopia, and in two of these the impairment of vision was more or less permanent (Oliver² and Lorant³). In these latter cases, however, the dosage of the drug seems to have been excessive.

RELATION OF NUMBER OF PNEUMOCOCCI TO CONCENTRATION OF ETHYLHYDROCUPREIN IN BACTERICIDAL TESTS

In the technic employed in the bactericidal tests we have used a fairly constant and rather small number of pneumococci per cubic centimeter. It seemed advisable to determine whether or not the degree of bactericidal action would be the same when a larger number of pneumococci are employed. Specimens of broth containing a small amount of ethylhydrocuprein in solution were therefore inoculated separately with two different amounts of the same culture and incubated at 37.5 C. At frequent intervals plates were prepared and counts were made of the colonies which developed after incubation.

Experiment 1.—Fifty c.c. of bouillon containing ethylhydrocuprein hydrochlorid 1 to 1,000,000 were inoculated with 0.01 c.c. of a twenty-four hour culture of *Pneumococcus* Type II and a like amount of the same bouillon with 1 c.c. of the same culture. Similarly, two flasks containing 50 c.c. of broth each but without ethylhydrocuprein were inoculated with 0.01 c.c. and 1 c.c. of the culture, respectively, as controls. All four cultures were incubated at 37.5 C. and bacterial counts were made at frequent intervals by making suitable dilutions and pouring plates with 20 c.c. dextrose agar. The results of the experiment are given in Table 5.

2. Oliver, G. H.: Brit. Med. Jour, 1916, **1**, 580.

3. Lorant, L.: Deutsch. med. Wchnschr., 1916, **42**, 1355.

TABLE 5.—NUMBER OF PNEUMOCOCCI IN RELATION TO ACTION OF ETHYLHYDROCUPREIN HYDROCHLORID

Incubation		Broth without Ethylhydrocuprein Inoculation 0.01 C.c.		Broth with Ethylhydrocuprein 1:1,000,000 Inoculation 0.01 C.c.		Broth without Ethylhydrocuprein Inoculation 1.0 C.c.		Broth with Ethylhydrocuprein 1:1,000,000 Inoculation 1.0 C.c.	
Hours	Minutes	No. of Viable Pneumococci per 0.5 C.c.	Log.	No. of Viable Pneumococci per 0.5 C.c.	Log.	No. of Viable Pneumococci per 0.5 C.c.	Log.	No. of Viable Pneumococci per 0.5 C.c.	Log.
0	0	28,000	4.447	19,050	4.379	2,455,000	6.390	2,450,000	6.389
2	0	19,300	4.285	11,450	4.05	2,870,000	6.457	1,685,000	6.226
4	0	9,750	3.989	475	2.676	7,050,000	6.848	1,005,000	6.002
5	30	11,450	4.058	37	1.568	22,500,000	7.352	625,000	5.795
7	0	11,850	4.073	3	0.047	26,500,000	7.423	370,000	5.568
9	0	34,500	4.537	0	0	49,500,000	7.694	210,000	5.322
11	35	625,000	5.795	0	0	67,500,000	7.829	100,000	5.000
25	..	49,500,000	7.694	0	0	55,500,000	7.744	240,000	5.380
48	51,000,000	7.707	45,000,000	7.653

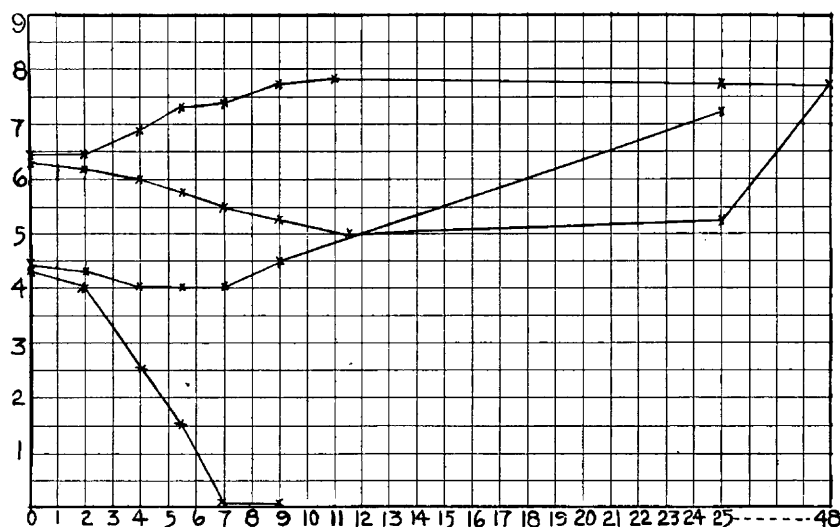


Diagram illustrating Experiment 1. Time in hours as abscissae at bottom, and at left logarithms of numbers of viable pneumococci per 0.5 c.c. as ordinates. A, Broth without ethylhydrocuprein. Inoculation 0.01 c.c. B, Broth with ethylhydrocuprein (1:1,000,000). Inoculation 0.01 c.c. C, Broth without ethylhydrocuprein. Inoculation 1 c.c. D, Broth with ethylhydrocuprein 1:1,000,000. Inoculation 1 c.c.

This experiment shows that while 19,050 pneumococci were all killed in nine hours in broth containing ethylhydrocuprein 1 to 1,000,000, 2,450,000 pneumococci were reduced to 100,000 in eleven hours and thirty-five minutes, but the surviving pneumococci were able to grow and in forty-eight hours multiplied approximately to the same extent (45,000,000) as in the control broth culture. The logarithms of the bacterial count are shown in Table 5. The results of Experiment 1 are shown graphically by plotting curves (Fig. 1), employing the time in hours as abscissa and the logarithms of the numbers of viable pneumococci per 0.5 c.c. of culture as ordinates.

PENETRATION OF ETHYLHYDROCUPREIN INTO FIBRINOUS EXUDATES

In the course of our clinical and experimental observations on ethylhydrocuprein, we have received the impression that the drug does not readily penetrate the alveolar exudate. The concentration of ethylhydrocuprein in the blood of patients receiving the drug, according to the dosage most commonly used by us, is about 1 in 500,000, as judged by the pneumococcal action of the serum in the test tube. If ethylhydrocuprein in this concentration were to thoroughly penetrate the alveolar exudate, it should destroy the pneumococci present therein, and one might therefore anticipate a shortening of the duration of the disease. Since the duration of the disease is not shortened the following experiment was devised to study the power of ethylhydrocuprein to penetrate a fibrinous clot.

Experiment 2.—Fifty c.c. of normal rabbit blood were drawn into 1 c.c. of sterile 20 per cent. sodium citrate solution ($2\text{Na}_2\text{C}_6\text{H}_5\text{O}_7 \cdot \text{H}_2\text{O}$) and centrifugalized. The supernatant plasma was drawn off and inoculated with a stock strain of *Pneumococcus* Type II (0.0001 c.c. of an eighteen-hour culture to 1 c.c. plasma) and 1.1 c.c. of sterile 9.5 per cent. calcium chlorid solution was then added and thoroughly mixed. The mixture was transferred to sterile cotton-plugged glass tubes 0.9 cm. in diameter, 2 c.c. being placed in each tube. A firm clot formed at the bottom of each tube in about one to one and a half hours at room temperature. To one of the tubes 1.6 c.c. of 0.85 per cent. saline solution was then added, covering the clot, and, in a similar manner, to each of the remaining tubes there was added 1.6 c.c. of saline solution containing a given concentration of ethylhydrocuprein hydrochlorid. The tubes were kept at room temperature for one-half hour, then incubated for twenty hours at 37.5 C., and examined. The number of organisms used for the incubation had been so chosen that the control tube which contained no ethylhydrocuprein showed small discrete colonies uniformly "peppering" the clot. In the tubes containing the more concentrated ethylhydrocuprein solutions no growth occurred in the upper portions of the clot. This was interpreted as due to the effect of the ethylhydrocuprein penetrating the clot in effective concentration to the depth of the zone of inhibition. The depth of the zone of inhibition bore a definite relationship to the concentration of the ethylhydrocuprein in the supernatant fluid. The zones of inhibition in the various tubes were measured and the results are shown in Table 6.

TABLE 6.—INHIBITION BY ETHYLHYDROCUPREIN OF GROWTH OF PNEUMOCOCCI IN FIBRINOUS CLOTS

Dilution of Ethylhydrocuprein	Depth in Mm. of Zones of Inhibition of Growth	Dilution of Ethylhydrocuprein	Depth in Mm. of Zones of Inhibition of Growth
1:100	10	1:10,000	5.5
1:500	9.5	1:50,000	3.5
1:1,000	9.0	1:100,000	2.5
1:5,000	6.0	1:200,000	1.75
1:10,000	5.5	1:300,000	1.25
1:50,000	3.5	1:400,000	1.0
1:100,000	2.5	1:500,000	0.0
1:500,000	0.0	1:600,000	0.0
1:1,000,000	0.0		
Control with saline	0.0	Control with saline	0.0

These experiments demonstrate that optochin, in the concentrations attainable with any degree of safety in the blood plasma of patients (about 1 in 500,000), possesses little power to penetrate a fibrinous clot. It is, therefore, possible that pneumococci in the interior of a pneumonic exudate may escape the action of ethylhydrocuprein, even though the drug be present in the blood stream in considerable concentration.

CLINICAL OBSERVATIONS

In discussing the effect of ethylhydrocuprein on the clinical course of the disease, the patients treated during the two years will be considered as one series. As previously, they will be analyzed from the standpoint of (*a*) the duration of the disease, (*b*) the occurrence of "spread" of involvement of lobes hitherto unaffected, (*c*) the effect of treatment on pneumococcemia and (*d*) mortality with reference to the immunologic classification of the infecting strain of pneumococcus.

(*a*). *Effect on Duration of Disease*.—Using the occurrence of a rectal temperature below 100 F. as a criterion for the termination of the acute attack, an arbitrary but serviceable standard, the average duration of the disease in all the recovered patients was eight days. No marked shortening, therefore, of the course of the disease can be said to have occurred in our series.

(*b*). *Occurrence of "Spread" of Pulmonary Lesion*.—Of the 75 cases, 20, or 26.6 per cent., showed a "spread" during treatment. In 14 of these 20 cases the serum of the patient possessed bactericidal power at the time the spread took place; this may be taken as presump-

tive evidence that the drug, although circulating in the blood in amounts sufficient to destroy pneumococci, does not pass into the alveolar spaces or exudate in amounts sufficient to destroy the bacteria there or inhibit their growth to any marked extent.

(c). *Pneumococcemia*.—In 23, or 30.6 per cent. of the 75 cases, viable pneumococci were present in the circulating blood at some time during the course of the disease. In many instances there were only a few pneumococci present, whereas in others there was a comparatively heavy blood infection. In 19 of the 23 cases the blood culture was positive before ethylhydrocuprein treatment was begun; in 4 of these the blood culture became negative during treatment with ethylhydrocuprein alone; 9 of the cases showed a progressively increasing number of micro-organisms while under treatment, and the remaining 6 died without subsequent blood cultures having been made. When in addition to ethylhydrocuprein immune serum was used in treatment, the number of pneumococci in the circulating blood was always reduced after the first administration of serum, but in one instance the number of micro-organisms later increased even though the patient received both ethylhydrocuprein and serum. In 4 instances the blood culture was negative at the time the ethylhydrocuprein treatment was instituted, but became positive later. From these results it may be stated that no marked beneficial effect of ethylhydrocuprein treatment was observed on the pneumococcemia of lobar pneumonia.

(d). *Mortality*.—Of the 75 patients treated, 28 died—a mortality rate of 37.3 per cent. Some of the patients were inadequately treated, judging from the production of pneumococcidal power in the serum. Moreover, in several cases treatment was instituted less than twenty-four hours before death and at a time when the patients were critically ill; the duration of administration of the drug in these cases was, therefore, too short to be of any value, considering the time required for its absorption and action. If all the patients who are known to have been inadequately treated, regardless of whether they died or recovered, be excluded, and also those cases in which treatment was instituted within twenty-four hours of death, or in which crisis occurred before the serum acquired bactericidal power, there would remain 51 cases, of whom 16 patients died—a mortality of 31.3 per cent. Of the 24 cases excluded from consideration 12 patients died and 12 recovered. The mortality rate in the 51 adequately treated patients, 31.3 per cent., does not show any considerable therapeutic effect from the use of the drug.

It should be stated that the series probably represents a group of very severe cases, for it is composed for the most part of cases due to infection with pneumococci of Types II and III, which we know are

the types responsible for the highest mortality rates. When the expected mortality in each of these groups (untreated) is compared with that actually encountered in the patients treated with ethylhydrocuprein, we find some reduction of mortality rate in the cases infected with pneumococci belonging to Group III, and no reduction in the cases due to pneumococci of Groups II and IV. This will be seen from a study of Table 7, in which the cases are arranged according to the type of infecting pneumococcus and in which the mortality obtained in the various groups in our series is contrasted with that obtained in a large series of patients not treated specifically and observed in different clinics.¹ One is forced to conclude from these figures that treatment with ethylhydrocuprein hydrochlorid failed to cause any reduction in the general mortality rate.

TABLE 7.—MORTALITY AMONG PATIENTS TREATED WITH ETHYLHYDROCUPREIN HYDROCHLORID COMPARED WITH THAT OF PATIENTS NOT SPECIALLY TREATED

Pneumo- coccus Type	Number of Patients Treated with Ethylhydro- cuprein	Recovered	Died	Mortality Rate Per cent.	Average Mor- tality Rate in Patients Not Specifically Treated
II	27	19	8	29.6	28
III	17	10	7	41.1	56
IV	6	5	1	16.6	16
Unclassified	1	1	0	0	..
	51	35	16	31.3	About 26

Of the 75 patients treated with ethylhydrocuprein, 14 in which the disease was caused by pneumococci belonging to Group II were treated, in addition, with the type homologous antipneumococcus serum. This agent was used in the form of the whole serum intravenously or the concentrated "extract"⁴ of the serum subcutaneously and intravenously. Of these 14 patients 10 recovered and 4 died, giving a mortality rate of 28.5 per cent., so that no reduction in the mortality rate was observed in cases of lobar pneumonia due to *Pneumococcus* Type II as a result of treatment with ethylhydrocuprein and antipneumococcus serum. The number of patients treated with serum and ethylhydrocuprein is too small, however, to permit of final conclusions on this point.

DISCUSSION

The experimental studies which we have here discussed and those previously reported show that ethylhydrocuprein hydrochlorid fulfills at least some of the requirements of a chemotherapeutic agent in lobar pneumonia. Even in high dilutions it kills the pneumococcus in

4. Chickering, H. T.: Jour. Exper. Med., 1915, **22**, 248.

the presence of body fluids. It is capable of being absorbed from the gastro-intestinal tract, and when injected into the muscles (Case 2947, Table 8) may pass into the blood stream. Moreover, when a sufficient amount is administered by mouth, represented by 0.024 to 0.028 gm. per kilogram of body weight per twenty-four hours, the blood serum becomes pneumococcidal *in vitro*, and furthermore, when such a condition obtains in the blood, the pericardial fluid also becomes pneumococcidal. The amount of the drug which it is necessary to administer in order to achieve this result, however, cannot always be given with safety to the patient, for in one instance in our series of cases total blindness lasting six days resulted, and in eight other instances there occurred visual symptoms of sufficient gravity to make the discontinuance of the drug necessary. A study of Table 8 would seem to suggest that where there is a comparatively heavy septicemia (for example, 100 colonies per 1 c.c. or over) a dosage of ethylhydrocuprein represented by 0.026 gm. per kilogram of body weight per twenty-four hours may be insufficient to produce pneumococcidal actions in the blood serum. It is possible that in such instances the drug may be fixed by the circulating pneumococci (Case Nos. 2845 and 2892). In only one case (No. 2822) which received 0.026 gm. of the hydrochlorid of the drug, or over, per kilogram of body weight per twenty-four hours in suitably divided doses did pneumococcidal action fail to appear in the serum.

When the cases in our series are analyzed from the standpoint of the effect of the drug on the duration of the disease, on the occurrence of "spread" of the lesion to previously uninvolved lobes of the lung, on the pneumococcemia and on the mortality rate, the results do not afford much support for the routine use of this drug in the treatment of acute lobar pneumonia.

It seems to us that the main reason why ethylhydrocuprein has not produced more striking results in the treatment of lobar pneumonia is because the toxicity of the drug is such as to keep the limits of dosage below the limits of effectiveness. If larger doses could be safely employed, it would be possible greatly to increase the amount of ethylhydrocuprein circulating in the blood. This would in turn undoubtedly increase the rate and degree of the resulting pneumococcidal action in the blood and might conceivably lead to a greater penetration of the drug into the consolidated portions of the lung. Our tests show that ethylhydrocuprein may be administered to patients in amounts sufficient to cause the serum to acquire pneumococcidal power. With the dosage that may be safely employed, however, the serum exhibits its bactericidal activity only at a slow rate, considerable time being required. Because of this fact the pneumococci in the body may be exposed for considerable time to concentrations of the drug insufficient to cause their destruction, particularly when they are protected by the

TABLE 8.—SUMMARY

Hospital Case Number	Age	Weight, Kg.	Type of Infecting Pneumococcus	Day of Disease When Ethylhydrocuprein Treatment Was Begun	Lung Involvement on Admission	Blood Culture Before Treatment	Method of Dosage of Ethylhydrocuprein in Periods of 24 Hrs.* Gm.	Amount of Ethylhydrocuprein per Kilo-gram of Body Weight per 24 Hrs. Gm.	Total Amount of Ethylhydrocuprein in Grams	Duration of Treatment in Days
2753	27	55.8	II	3	L. L.	Sterile	0.45+7×0.15; 10×0.15	0.0269	5.7	4
2754	13	39.6	II	8	L. U. L. L.	0.3+7×0.1; 10×0.1	0.0252	2.3	2¼
2783	48	63.3	III	7	R. U. R. L.	Positive; 325 col. per 1.0 c.c.	0.45+0.25+0.3; 2×0.15; base	1.3	½
2786	34	42.7	II	8	R. U.	Sterile	0.3+0.2+7× 0.10; 10×0.1; base	0.028	2.2	2
2797	67	78.2	III	2	R. U.	Sterile	0.6+2×0.25+6 ×0.15; 11×0.2	0.023	10.8	3
2800	42	78.9	III	4	L. L.	Sterile	0.6+0.3+8× 0.2; 1.65 in 2nd 24 hrs.	0.03	4.15	2
2812	74	58.5	III	2	L. L.	Sterile	0.6+8×0.15; 12×0.15	0.03	3.0	2
2822	13	37.2	II	6	L. L.	Sterile	0.2+7×0.1; 9× 0.1; 10×0.1	0.0241	3.6	4
2762	23	70.0	III	3	R. L.	Sterile	0.45+8×0.15; 3×0.5 per rectum	0.0235	3.15	2
2825	50	69.0	II	2	L. L.	Positive; 3 col. per 1 c.c.	0.6+8×0.15; 12×0.15	0.026	6.5	4
2827	29	52.6	II	3	L. L. L. U.	Positive; 2,000 cols. per 1 c.c.	0.45+2×0.15	0.0285	0.75	¼
2831	35	57.0	II	5	L. L.	Sterile	0.45+7×0.15; 10×0.15	0.0263	1.65	1
2834	28	58.4	II	5	L. L.	Sterile; 16 hrs. after ethylhydrocuprein positive—12 col. per 1 c.c.	0.5+0.2+6× 0.15; 9×0.15; 10×0.15	0.0274	9.05	6
2837	48	46.0	III	2	R. L.	Sterile	0.45+7×0.15; 7×0.2	0.0326	2.9	2

* Given by mouth unless otherwise stated; hydrochlorid used unless otherwise stated.

OF CASES

Time of Appearance of Bactericidal Action in Serum after Initial Dose of Ethylhydrocuprein	Duration of Disease in Days	Toxic Symptoms Referable to Ethylhydrocuprein	Complications	Occurrence of "Spread" During Treatment	Result	Remarks
Not studied	7	None	None	None	Recovered	
Not studied	10	None	Pericarditis	None	Death	
No B. A.	7	None	Pericarditis	None	Death	Blood culture 8 hours after treatment showed innumerable colonies per 0.5 c.c. blood
No B. A.	9	None	None	None	Recovered	
20 Hrs.	7	None	None	Spread to right lower	Death	
11 Hrs.	6	None	None	None	Death	Blood culture 24 hours after treatment was begun showed 23 colonies per 1.0 c.c. blood; pericardial fluid showed bactericidal action
6 Hrs.	6	Temporary blindness, deafness and tinnitus	None	None	Death	Ethylhydrocuprein discontinued on account of eye symptoms
No B. A.; slight temporary inhibition	10	None	None	None	Recovered	
5 Hrs.	5	Persistent vomiting; partial deafness	None	None	Recovered	
5.5 Hrs.	5	None	None	None	Death	Progressive increase in septicemia during treatment. "Fast" strains recovered from blood; antipneumococcus serum 85 c.c. intravenously on last day
Not studied	4	None	None	None	Death	
11 Hrs.	6	None	None	None	Recovery	75 c.c. antipneumococcus serum intravenously
11 Hrs.	11	None	None	Spread to right lower	Death	Active maniacal delirium. Blood culture positive 16 hours after ethylhydrocuprein was started; 1,015 c.c. antipneumococcus serum intravenously
Within 24 Hrs.	4	Transient deafness; slight dimness of vision after Temp. had become normal	None	None	Recovery	Ethylhydrocuprein discontinued after temp. became normal on account of eye symptoms. Eye grounds apparently normal on ophthalmoscopic examination at time patient complained of dimness of vision

TABLE 8.—SUMMARY

Hospital Case Number	Age	Weight, Kg.	Type of Infecting Pneumococcus	Day of Disease When Ethylhydrocuprein Treatment Was Begun	Lung Involvement on Admission	Blood Culture Before Treatment	Method of Dosage of Ethylhydrocuprein in Periods of 24 Hrs.* Gm.	Amount of Ethylhydrocuprein per Kilogram of Body Weight per 24 Hrs. Gm.	Total Amount of Ethylhydrocuprein in Grams	Duration of Treatment in Days
2838	45	48.8	III	4	R. L.	Sterile	0.5+5×0.2; 8×0.2; 6×0.25	0.0307	7.6	5
2845	46	40.4	II	5	R. U.	Positive; 1,000 col. per 1 c.c.	0.5+4×0.25; 6×0.25	0.0371	2.0	1½
2849	42	94.4	III	4	R. U.	Positive; 1 col. in 3 c.c.	0.5+4×0.25; 6×0.25	0.0158	2.0	1½
2865	23	60.4	II	4	L. U.	Sterile	0.45+7×0.15; 10×0.15	0.0248	5.25	4
2869	31	66.6	II	2	R. L.	Positive; 400 col. per 1 c.c.	0.45+7×0.15; 10×0.15	0.0225	5.3	4
2870	46	56.8	II	4	L. L.	Sterile	0.45+7×0.15; 8×0.15	0.0263	2.7	2
2879	26	79.0	II	3	L. L.	Positive	0.5+9×0.15; 10×0.15	0.0234	3.45	2
2885	42	49.0	II	3	R. U.	Sterile	0.45+7×0.15	0.0300	1.95	1½
2886	21	59.8	II	4	L. U.	Sterile	0.45+7×0.15; 11×0.15	0.0250	5.25	4
2892	41	59.0	II	5	R. U.	Positive; 100 col. per 1 c.c.	0.45+7×0.15; 10×0.15	0.0254	2.25	1½
2890	28	35.5	II	4	R. L.	Positive; 3 col. per 1 c.c.	0.45+8×0.15; 10×0.15	0.0464	5.4	4
2897	34	59.0	II	4	L. U.	Sterile	0.45+7×0.15; 10×0.15	0.0254	6.0	4
2898	32	53.2	III	5	L. L.	Positive; 120 col. per 1 c.c.	0.45+7×0.15; 10×0.15	0.0283	3.75	3
2911	50	74.2	III	3	R. U.	Sterile	0.45+7× 0.15+1×0.1; at rate of 10×0.15 thereafter	0.021	2.95	2

* Given by mouth unless otherwise stated; hydrochlorid used unless otherwise stated.

OF CASES

Time of Appearance of Bactericidal Action in Serum after Initial Dose of Ethylhydrocuprein	Duration of Disease in Days	Toxic Symptoms Referable to Ethylhydrocuprein	Complications	Occurrence of "Spread" During Treatment	Result	Remarks
Within 24 Hrs.	9	None	None	None	Recovery	
No B. A.; temporary inhibition only	7	None	None	None	Death	Pericardial fluid showed bactericidal action; 300 c.c. antipneumococcus serum intravenously
No B. A.	5	None	None	None	Death	Blood culture before death, 1,000 colonies per 1.0 c.c. blood
Within 24 Hrs.	7	None	None	None	Recovery	
No B. A.	6	None	None	Spread to right upper	Death	Blood culture constantly positive; 10,000 colonies per 1.0 c.c. just before death; 580 c.c. antipneumococcus serum intravenously
Within 24 Hrs.	9	Transient amblyopia and deafness	None	None	Recovery	Ethylhydrocuprein discontinued on onset of amblyopia
No B. A.; slight temporary inhibition	5	None	None	None	Recovery	Blood culture became negative during treatment; 440 c.c. antipneumococcus serum intravenously
Within 12 Hrs.	8	Transient amaurosis and tinnitus	None	None	Recovery	Ethylhydrocuprein discontinued on account of eye symptoms; 770 c.c. antipneumococcus serum intravenously; delayed resolution
Within 12 Hrs.	8	Slight deafness	None	None	Recovery	
No B. A.; slight temporary inhibition	7	None	None	Spread to right lower	Death	Blood culture before death, 600 colonies per 1.0 c.c. blood
Within 24 Hrs.	8	None	Pneumococcal meningitis	Spread to left lower	Death	Blood culture 18 hours after ethylhydrocuprein was commenced showed 14 colonies per 1 c.c.; 1,300 c.c. serum intravenously; 80 c.c. serum intraspinaly; 30 c.c. concentrated serum subcutaneously
Within 12 Hrs.	8	None	None	None	Recovery	380 c.c. serum intravenously; 74 c.c. conc. serum subcutaneously
Within 24 Hrs.	8	None	None	Spread to right lower	Death	
Complete inhibition	8	Temporary blurring of vision and temporary partial deafness	None	None	Recovery	Ethylhydrocuprein discontinued on account of eye symptoms

TABLE 8.—SUMMARY

Hos- pital Case Num- ber	Age	Weight, Kg.	Type of Infec- ting Pneu- mo- coccus	Day of Disease When Ethyl- hydro- cuprein Treat- ment Was Begun	Lung Involve- ment on Admis- sion	Blood Culture Before Treatment	Method of Doseage of Ethyl- hydro- cuprein in Periods of 24 Hrs.* Gm.	Amount of Ethyl- hydro- cuprein per Kilo- gram of Body Weight per 24 Hrs. Gm.	Total Amount of Ethyl- hydro- cuprein in Grams	Dura- tion of Treat- ment in Days
2919	35	49.8	III	4	L. L.	Sterile	0.45+7×0.15; 10×0.15	0.03	6.30	4
2922	30	58.0	II	4	L. L.	Sterile	0.45+7×0.15; 10×0.15	0.0258	11.1	8
2926	19	46.0	II	5	R. U.	Sterile	0.45+5×0.15; 7×0.15	0.026	3.0	2½
2927	22	56.4	III	3	R. L.	Sterile	0.45+7×0.15; 8×0.15	0.0265	4.95	4
2940	31	74.2	IV	7	L. U.	Positive; 4 col. per 1 c.c.	0.5+10×0.15; 12×0.15	0.0269	3.05	2
2943	22	44.4	II	5	R. L.	Sterile	0.4+8×0.1; 12×0.1	0.027	4.9	4
2946	28	62.6	II	4	R. U.	Sterile	0.5+8×0.15; 12×0.15	0.0271	12.8	8
2947	51	70.4	III	6	R. L.	Positive	0.7 intra- muscularly + single dose of 1.8 gm. intramus- cularly	0.0355	9.9	5
2973	40	50.2	III	3	R. U.	Sterile	0.45+7×0.15; 10×0.15	0.0375	3.15	3
2972	19	55.6	II	1	L. L.	Sterile	0.45+7×0.15; 10×0.15	0.0269	6.55	4½
2991	49	71.2	II	2	R. L.	Sterile	0.45+9× 0.15; 6×0.3	0.025	14.4	8
3006	35	46.8	II	3	R. L.	Sterile	0.45+7×0.15; 10×0.15	0.032	7.8	5
3015	47	75.8	III	3	L. L.	Sterile	0.6+10×0.2	0.034	2.2	1
2868	20	57.0	II	5	R. L.	Sterile	0.45+7×0.15	0.0263	1.5	1
3031	38	57.0	II	3	L. L.	Positive; 80 col. per 1 c.c.	0.45+8×0.15; 9×0.15; 10×0.15	0.028	6.3	5½

* Given by mouth unless otherwise stated; hydrochlorid used unless otherwise stated.

OF CASES

Time of Appearance of Bactericidal Action in Serum after Initial Dose of Ethylhydrocuprein	Duration of Disease in Days	Toxic Symptoms Referable to Ethylhydrocuprein	Complications	Occurrence of "Spread" During Treatment	Result	Remarks
Within 12 Hrs.	9	None	None	Spread	Death	Pericardial fluid showed bactericidal action; blood culture sterile post-mortem
12 Hrs.	14	None	None	Spread to left upper	Recovery	197 c.c. conc. serum subcutaneously
12 Hrs.	8	Slight deafness	None	None	Recovery	
12 Hrs.	6	Temporary deafness	None	Spread to left upper	Recovery	
10 Hrs.	11	Dimness of vision and tinnitus	None	Death	Ethylhydrocuprein discontinued on account of eye symptoms; eye symptoms disappeared
10 Hrs.	10	None	None	Spread to right upper	Recovery	
12 Hrs.	12	None	None	Spread to right lower	Death	Blood culture shortly before death yielded innumerable colonies
6.5 Hrs.	?	None	Empyema	Spread to left lower	Operation; death 60 days after admission	Blood culture became negative; intermission of 90% hours in ethylhydrocuprein treatment after 2.5 gm. had been given
Within 24 Hrs.	6	Temporary deafness	None	None	Recovery	
Within 24 Hrs.	6	Slight transient blurring of vision after temp. had become normal	None	None	Recovery	
Not studied	9	Temporary deafness	Delayed resolution	None	Recovery	
Within 12 Hrs.	8	None	None	Spread to left lower	Death	
Within 12 Hrs.	?	Temporary blindness	None	None	Recovery	Ethylhydrocuprein discontinued on account of visual symptoms
Not studied	12	None	None	None	Recovery	Ethylhydrocuprein discontinued because it was thought that patient had had crisis
Within 12 Hrs.	8	None	None	None	Death	Strain obtained just after death was not "fast" to ethylhydrocuprein; pericardial fluid obtained post-mortem showed pneumococidal action for Type I pneumococcus

comparative impenetrability of a solid pneumonic exudate. Under such circumstances, as we have shown, pneumococci may become resistant or "fast" to the action of the drug.

As our experiments indicate, there seems to be some relationship between the number of pneumococci and the concentration of ethylhydrocuprein which is required to completely kill them. Thus, in test tube experiments it has been shown that whereas a given amount of the drug in solution is sufficient to destroy a given number of pneumococci per unit volume, the same amount of drug is not able to destroy 100 times this number in the same volume. Inasmuch as we cannot estimate in any human case the number of pneumococci which it is necessary to destroy, it is quite conceivable that much larger amounts of the drug than we have found it safe to administer may be necessary to produce the required concentration in the body fluids.

Finally, it is probable that in the concentration which may safely be attained in the blood stream of the patient (about 1 in 500,000), the drug does not penetrate the alveolar exudate to any marked degree and therefore cannot kill the pneumococci there present.

Our conception of the present status of ethylhydrocuprein therapy in lobar pneumonia is, then, that while much of the experimental evidence is favorable, the clinical results that have been obtained are scarcely sufficient to warrant the routine administration of a drug the use of which may result in damage to vision. Probably the drug would be efficient if it could be given in larger amounts. As a "lead" in chemotherapy the drug is of great value; synthetic study of the quinin alkaloids should be made for a compound possessing greater pneumococidal power in the presence of body fluids, greater velocity of action on pneumococci and less toxicity. Such a compound should, in addition, possess the power of rapid and easy penetration into the alveolar exudate. With such a drug at our disposal we might expect in lobar pneumonia something approaching a *therapia sterilisans magna*.

CONCLUSIONS

1. Ethylhydrocuprein (optochin) base is absorbed with difficulty into the blood stream from the gastro-intestinal tract; the hydrochlorid of the drug is readily absorbed.
2. During treatment with ethylhydrocuprein pneumococci in the human body can gradually become "fast" or resistant to its action.
3. The pericardial fluid obtained post mortem from patients treated with ethylhydrocuprein hydrochlorid showed pneumococidal power.
4. The serum of one patient who received a very large dose of ethylhydrocuprein hydrochlorid intramuscularly showed pneumococidal power (Case 2947, Table 8).

5. Among seventy-five patients treated with ethylhydrocuprein there were nine who showed some degree of amblyopia (12 per cent.); this was mild in three cases and more severe in six. In all those who recovered from the pneumonia, the eye symptoms disappeared completely after the administration of the drug had been discontinued.

6. The systematic use of ethylhydrocuprein (optochin) in the treatment of seventy-five cases of acute lobar pneumonia due to pneumococci did not lead to any noteworthy therapeutic benefit. The failure of the ethylhydrocuprein treatment to influence favorably the course of the disease is probably due to the following:

(a). It is impossible to administer a sufficient amount of the drug to produce an effective concentration in the blood stream without at the same time exposing the patient to the danger of toxic action.

(b). The rate of the pneumococcal action of ethylhydrocuprein is too slow in the concentrations which may be attained in the blood stream of the patient with any degree of safety; pneumococci, therefore, may gain access to the circulating blood at a greater rate than they are destroyed therein, even though the serum show pneumococidal action.

(c). In the concentrations which are safely attained in the body fluids the drug probably penetrates but poorly into the alveolar exudate.

7. The routine use of ethylhydrocuprein in the treatment of acute lobar pneumonia cannot be recommended.