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## THE TREATMENT OF LOBAR PNEUMONIA WITH CONCENTRATED ANTIPNEUMOCOCCUS SERUM\*

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During the past two years we have continued our studies on the specific treatment of lobar pneumonia at Bellevue Hospital. This work has been both clinical and experimental. Since the fall of 1926, our interest has been largely confined to investigation of the immunologic properties and the therapeutic value of concentrated antipneumococcus serum. The serum that has particularly engaged our attention is a derivative of antipneumococcus serum prepared according to the method of Felton.<sup>1</sup>

### PREPARATION AND STANDARDIZATION OF SERUM

The actual technic of the preparation of this serum has been thoroughly described by Felton in a series of articles which he has published in various periodicals. The original antipneumococcus horse serum is concentrated in both the monovalent and the polyvalent forms. Felton's method of concentration may be briefly described as follows.<sup>2</sup>

One liter of serum is slowly poured into 15 liters of agitated, cooled distilled water, and the precipitate is allowed to settle over night in the icebox. The supernatant fluid is then siphoned off, and the flocculent precipitate is washed with the same volume of cooled, distilled water used for the precipitation. The suspension is again permitted to settle for twenty-four hours. Once more, the supernatant liquid is siphoned off and the white sediment collected by means of a Sharpless centrifuge. The compact white residue in the bowl of the centrifuge is taken out and dissolved in one-half molecular sodium chloride. If the solution is not clear, it is then passed through a Berkefeld candle. The resulting filtrate is a slightly opalescent fluid, free from sediment. By the use of this technic on a number of different antipneumococcus serums, concentrates several times stronger in immune bodies than the original serum were obtained. Even greater concentration, however, has been secured by using other solvents than sodium chloride, such as tartaric acid.

\* This study received financial aid from the Metropolitan Life Insurance Company's Influenza Fund.

From the Second Medical (Cornell) Division and the Pathological Department of Bellevue Hospital, and the Hygienic Laboratory of the U. S. Public Health Service.

1. Felton, L. D.: A Study of the Isolation and Concentration of the Specific Antibodies of Antipneumococcus Sera, Boston M. & S. J. 190: 819-822 (May) 1924; The Protective Substance in Antipneumococcus Serum: I. Type I Serum, J. Infect. Dis. 37: 199-224 (Sept.) 1925; II. Effect of Certain Chemical Manipulations on the Stability of the Protective Substance in Type I Antipneumococcus Serum, *ibid.* 37: 309-320 (Sept.) 1925; III. The Protective Substance in Types I, II and III Antipneumococcus Serum, Bull. Johns Hopkins Hosp. 33: 33-60 (Jan.) 1926.

2. Personal communication to the authors.

Felton's serum is therefore an aqueous solution of pneumococcus antibodies containing the globulins and a few other inert substances. The nitrogen content varies from 8 to 15 mg. per cubic centimeter, which is about the same as that of blood serum. The finished product is a slightly opalescent solution with a specific gravity of 1.032, containing a small amount of preservative.

During the latter part of this investigation we worked with another refined antipneumococcus serum prepared by Banzhaf,<sup>2</sup> as follows:

Serum or plasma is saturated with sodium chloride and the resultant precipitate is filtered off. To the filtrate is added one-half volume of saturated ammonium sulphate solution to precipitate the pseudoglobulins and antibodies. This precipitate is filtered off and dialyzed free from salts.

The dialyzed product is added to distilled water and the whole adjusted to pH 5.6 to precipitate the antibodies. The antibodies are then redissolved in 1 per cent sodium chloride and the solution is passed through a Berkefeld filter.

These two concentrated serums, though prepared by different chemical methods, are practically identical as regards their physical and immunologic properties. The refined serums were prepared partly in the research laboratories of the New York City Board of Health and partly in the laboratories of the Department of Hygiene of Harvard University, and were supplied to us by Dr. William H. Park and Dr. Milton J. Rosenau, to both of whom we are greatly indebted.

Felton has worked out a method of standardizing antipneumococcus serum in terms of a unit. Instead of using fixed amounts of serum against varying amounts of pneumococcus culture, Felton titrates varying amounts of serum against a fixed amount of culture. The unit is that amount of serum necessary to protect a mouse against 0.05 cc. of a 1:10 dilution of an eighteen hour broth culture of pneumococcus, which is usually equivalent to at least 1 million lethal doses.

### POTENCY OF CONCENTRATED SERUM

One of the first points to be determined in this study was the relative potency of concentrated serum as compared with ordinary antipneumococcus serum. In order to settle this question, the following experiment was carried out on eight normal human subjects:

The blood of the eight persons was first tested for protective power, four against pneumococcus type I and four against pneumococcus type II. None of the subjects showed specific protective bodies before the experiment. Two men then received unconcentrated type I antipneumococcus serum, the first subject 1 cc., or 800 units, and the second 10 cc., or 8,000 units, intravenously. Two other men received 1 cc., or 2,000 units, and 10 cc., or 20,000 units, respectively, of concentrated type I antipneumococcus serum. Thirty minutes after the injections, blood was taken from each person for the determination of protective power.

In table 1 it will be noted that the subjects who received the refined serum showed a distinctly higher protection than that of the men injected with ordinary antipneumococcus serum. This was also true when a similar comparison was made between a standard type II serum and a refined type II serum (table 1). Of course these tests are only a rough measure of potency, but they show clearly that both type I and

typed, we sent a carefully collected specimen of sputum to the laboratory for bacteriologic study as soon as a probable diagnosis of lobar pneumonia was made. In every case the sputum was typed by the mouse method. In addition to this, many patients were studied by means of blood cultures, precipitin tests on the urine and the Krumwiede sputum test. Wherever there was any doubt as to the reaction obtained in the mouse exudate, a second specimen of sputum was collected and studied by the mouse method. During the latter part of the work, the typing was checked by diagnostic serum from two different laboratories. In all cases in which no agglutination or precipitation was present for any one of the three fixed types, one or more control specimens of sputum were studied before the case was finally relegated to the miscellaneous group. In order to avoid such errors as the inclusion of streptococcus and Friedländer bacillus infection in miscellaneous group IV, blood agar plate cultures were made from every mouse exudate. In nineteen cases an organism was obtained which gave atypical reactions with type II immune serum. As the group was small and its significance doubtful, it has been disregarded in the following discussion of serum treatment. Every case of lobar pneumonia admitted to the wards was given a number as soon as the diagnosis of lobar pneumonia had been made.

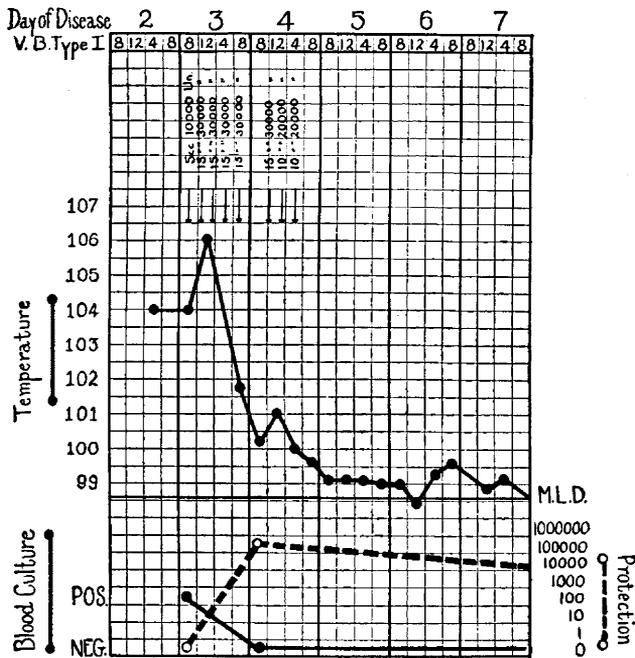


Chart 1.—Type I pneumonia, treated with concentrated serum.

type II refined serums are more potent than the unrefined antipneumococcus serums.

The refined antipneumococcus serum, like the original unconcentrated antipneumococcus serum, has the power of sterilizing the blood of monkeys infected experimentally with pneumococcus type I lobar pneumonia. In an experiment carried out in our laboratory, four monkeys were given many times the lethal dose of

TABLE 1.—Protection Produced in Normal Human Subjects by Immune Serum and by Refined Immune Serum

Type of Pneumonia	1 Cc. Immune Serum	1 Cc. Refined Immune Serum	Ratio	10 Cc. Immune Serum	10 Cc. Refined Immune Serum	Ratio
<b>Type I</b>						
Potency of serums (units)	800 units	2,000 units	1:2.5	8,000 units	20,000 units	1:2.5
Protection in subject	1,000 M.L.D.	10,000 M.L.D.	1:10	10,000 M.L.D.	100,000 M.L.D.	1:10
<b>Type II</b>						
Potency of serums (units)	320 units	800 units	1:2.5	3,200 units	8,000 units	1:2.5
Protection in subject	100 M.L.D.	100,000 M.L.D.	1:100	10,000 M.L.D.	1,000,000 M.L.D.	1:100

pneumococcus type I intratracheally. All four monkeys developed pneumonia and septicemia. When three of the monkeys were treated with small intravenous injections of concentrated serum, the blood was promptly sterilized and the animals recovered. The control monkey did not receive any serum and died on the fourth day with a massive pneumococcus septicemia.

Realizing that the value of an experiment of this kind depends largely on the accuracy with which the sputum is

ADMINISTRATION OF SERUM

The serum was administered as follows: In every patient with an even number, treatment was instituted promptly with polyvalent serum. If sputum was obtainable, it was sent at once to the laboratory for typing, but as the type determination usually took from twelve to eighteen hours, it was deemed advisable to start treatment with polyvalent serum without waiting for the laboratory report on pneumococcus type. Patients with odd numbers did not receive serum of

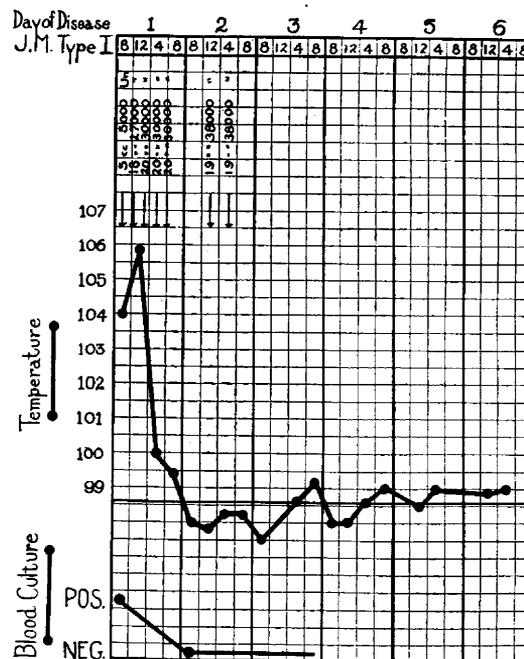


Chart 2.—Type I pneumonia, treated with concentrated serum.

any kind, but in other respects were treated in the same way as the patients who received serum.

In order to avoid anaphylactic accidents, each patient was first questioned as to previous injections of horse serum and as to hay-fever, asthma or hives. An intradermal and an ophthalmic test were then made with a 1:10 dilution of normal horse serum. If after fifteen minutes these tests were both negative, 5 cc. of concentrated serum was slowly injected intravenously.

The rule was to devote five minutes to the injection of 5 cc. of serum. If the patient did not show any reaction to this first injection of serum, a second injection of 15 or 20 cc. was given intravenously from one to two hours later, and this dose was repeated in another two to three hours. An effort was made to inject approximately 100 cc. of serum during the first twenty-four hours. One hundred cubic centimeters was gen-

number of units than type I patients, because of the inferior strength of type II serum.

The efforts to begin treatment promptly were only fairly successful. One fourth of the treated patients received their first dose of serum within six hours after admission, while one half of the treated patients

TABLE 2.—Dosage of Serum Administered to Treated Patients

Dosage of Concentrated Serum in Units	Number of Patients			Number of Patients		
	Type of Patients			Type of Patients		
	Type I	Type II	Types I & II	Type I	Type II	Types I & II
0-20,000.....	5	15	20	10	5	15
20,000-50,000.....	15	20	35	26	12	38
50,000-100,000.....	22	22	44	33	18	51
100,000-200,000....	43	17	60	55	29	84
200,000-400,000....	33	17	50	13	25	38
More than 400,000	13	6	19	5	8	13
	131	97	228	142	97	239

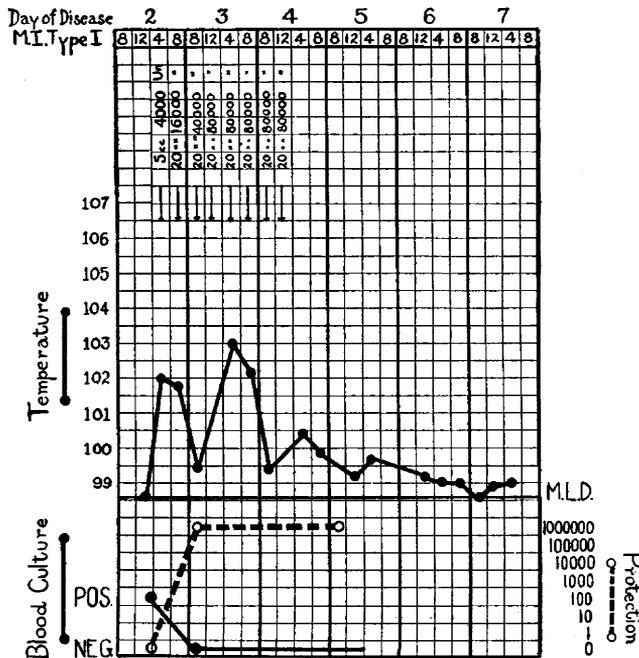


Chart 3.—Type I pneumonia, treated with concentrated serum.

erally equivalent to at least 100,000 units against type I, and to an almost equal number against type II. The potency of the polyvalent serum against type III has been either nil or so low as to be of comparatively small practical value.

The amount of serum administered on the following day was determined by the clinical condition of the patient. If his general condition had improved and if the chart showed a decided drop in temperature, pulse rate and respiration rate, the amount of serum administered was usually considerably less than that given on the first day, that is, two or three 20 cc. injections instead of four or five as on the previous day. If, on the other hand, the patient's condition was worse or if it remained unchanged, the intensive treatment was continued. On the third day the same policy was pursued. If the patient's temperature was under 100 F. and his condition was good, the general rule was to give one or possibly two of the 20 cc. injections. If he remained ill, the intensive treatment was continued until death or crisis occurred.

Three hundred and ninety-six of the 441 patients given even numbers actually received serum. The discrepancy is due chiefly to the fact that for a certain period in the first year of the experiment, the type III and the miscellaneous group IV patients were not treated with serum, though they were classified in the treated series. The amount of serum and its potency in units that pneumococcus type I and type II patients received is shown in table 2. The great majority of the patients (75.8 per cent) for whom potent serum was available received an adequate amount as measured in units of potency. Type II patients received a smaller

received their first injection later than six hours, but within twenty-four hours after admission. The average time elapsing between admission to the hospital and the first dose of serum was eighteen hours.

REACTIONS

Two types of reactions have been noticed after the intravenous injection of concentrated serum—thermal and allergic. Thermal reactions have been compara-

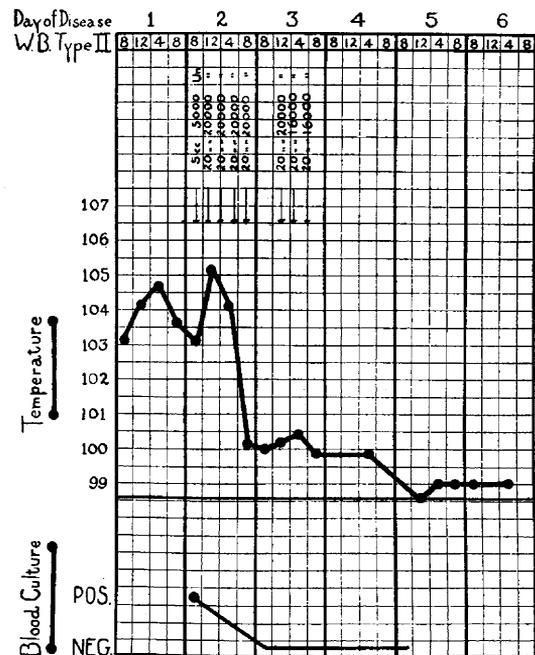


Chart 4.—Type II pneumonia, treated with concentrated serum.

tively rare. Of the patients who received concentrated serum 15.4 per cent have had one or more chills, but nearly all of these occurred after the use of certain lots of concentrated serum. Some lots of Felton's serum have never given a thermal reaction. The chills have nearly always been of a mild type, and never appeared to have any injurious effect on the patient. The allergic reactions have nearly always occurred after the first intravenous injection of 5 cc. or less of

serum. In a few patients who had already received several doses of serum, a reaction occurred when 20 cc. of a new lot of serum was administered (two cases), or when the dose of serum was sharply increased above the amount of the previous injection (two cases). The immediate allergic type of reaction manifested itself in the following way: From three to fifteen minutes after the injection of serum the patient's face became flushed, the respiration rate more rapid and the dyspnea

less, serum sickness occurred in five, or 4.9 per cent, while in those who received more than 50 cc. of refined serum, serum sickness occurred in forty-seven patients, or 27.2 per cent.

RESULTS OF TREATMENT

The results of the utilization of any therapeutic agent in the treatment of lobar pneumonia have to be determined by its clinical effect on the course of the disease and its influence on the death rate. In the 441 cases of pneumococcal pneumonia which comprise the treated series, there are many charts which demonstrate in a striking way the clinical effect of concentrated serum on the course of the disease. This applies particularly to the type I group, but is true to a lesser extent of type II infections. The best examples of immediate clinical effect were seen in those patients who were treated with serum on the first, second or third day of the disease.

From a large group of cases in which a definite change in the condition was manifest following the administration of serum, we have selected the following illustrations:

REPORT OF CASES

CASE 1.—V. B., a man, aged 23 (chart 1), who had pneumococcus type I pneumonia, entered the hospital on the second day of his disease. A mild bacteremia was demonstrated. Treatment was begun eighteen hours after admission, 200,000 units being given in 100 cc. of serum during the ensuing thirty-two hours. There was a prompt fall in temperature, sterilization of the blood and establishment of protection in the patient's blood.

CASE 2.—J. M., a youth, aged 18 (chart 2), had pneumococcus type I pneumonia, with a positive blood culture. The patient was treated with concentrated antipneumococcus serum on the first day of his disease. The response to serum was quick and permanent.

CASE 3.—M. I., a man, aged 23 (chart 3), had a fairly severe bacteremia, with eighty-nine colonies of type I pneumococci per cubic centimeter of blood on the second day of the disease.

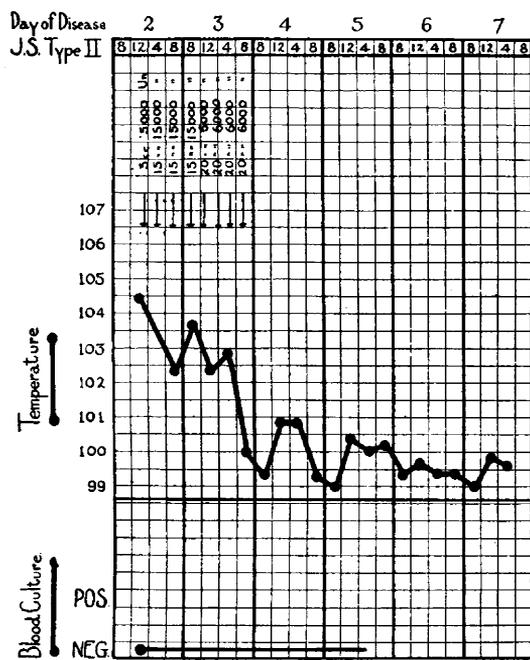


Chart 5.—Type II pneumonia, treated with concentrated serum.

more marked. The severe cases showed some cyanosis. The expression was anxious and occasionally the patient complained of precordial pain. Every one of these patients developed a simultaneous urticaria. One third of the allergic reactions manifested themselves as urticaria without any other symptoms. During the winter of 1926-1927 the incidence of immediate allergic reactions was 10.2 per cent. During the winter of 1927-1928 the incidence was 3.9 per cent, and most of the latter reactions followed the use of serums prepared in 1926-1927. This suggests that many of the apparently allergic reactions may have been due to a substance in the serum capable in itself of exciting a reaction in a nonsensitive individual.

None of the patients who had anaphylactic symptoms died during the attack. One patient who was already quite ill with pneumonia died seven hours after the anaphylactic reaction and the question was naturally raised whether the reaction had been a factor in the unfavorable termination. In almost every instance the prompt administration of epinephrine subcutaneously relieved the patient of his unpleasant symptoms in the course of a few minutes.

Serum sickness developed in fifty-two, or 18.8 per cent, of the treated patients, as compared with approximately 50 per cent of patients<sup>3</sup> treated with standard antipneumococcus serum. The likelihood of a patient's developing serum sickness seemed to depend in great measure on the amount of refined serum administered. Among patients receiving 50 cc. of refined serum or

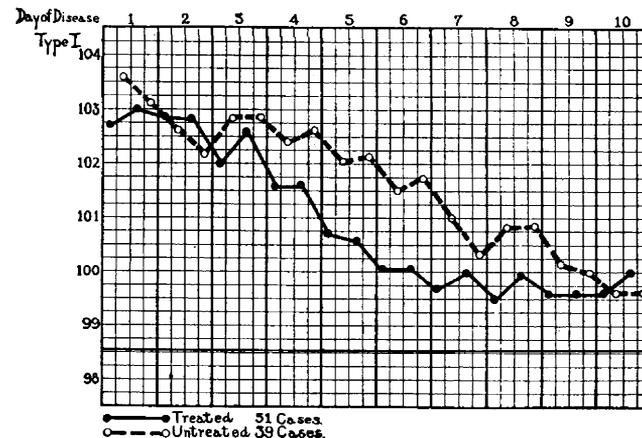


Chart 6.—Mean temperature curve of patients, treated and untreated, admitted during first three days of type I pneumonia.

Following treatment with concentrated serum, blood cultures became sterile and a high degree of protection was present in the blood serum. This coincided with a marked relief of symptoms and a fall in temperature.

CASE 4.—W. B., a man, aged 40 (chart 4), who had pneumococcus type II pneumonia, was admitted to the hospital on the first day of the disease. Treatment was begun twenty-four hours later, when a blood culture was weakly positive. No further observations were made of the blood cultures or protective bodies in this patient, but the marked and prompt

3. Cole, Rufus, in Nelson's System of Medicine, New York 1: 266, 1920.

change in his general condition and the fall in temperature were quite striking.

CASE 5.—J. S., a man, aged 23 (chart 5), who had pneumococcus type II pneumonia, was seen and treated on the second day of the disease. The initial blood culture before treatment was negative. The apparent response to serum was marked.

EFFECT OF SERUM ON SEPTIC PATIENTS

Numerous writers on the specific treatment of pneumonia have stressed the importance of antipneumococcus serum in sterilizing the blood in type I pneumonia. Cecil and Steffen,<sup>4</sup> and more recently Baldwin,<sup>5</sup> have pointed out the fact that a potent type II antipneumococcus serum possesses the faculty of sterilizing the blood in type II pneumonia, provided the sepsis is not too marked. In the present study, blood cultures were taken from 179 patients in the treated series and 121 patients in the control series. In fifty-one treated type I and type II cases with positive blood cultures, the death rate was 62.8 per cent, while in forty-five untreated cases of type I and type II pneumonia, the death rate was 71.2 per cent. Judging from these figures as they stand, the serum did not appear to have a very marked effect on the septic patient, but it was interesting to note that in fifty-five treated cases of type I and type II pneumonia with sterile blood cultures the death rate was 27.3 per cent, while in twenty-nine untreated cases with sterile blood cultures the death rate was 20.7 per cent. In both series figures are misleading by reason of the fact that in both treated series the patients selected for blood culture were usually very ill. In 153 treated patients who were not studied by blood cultures, the death rate was 18.9 per cent, in contrast to a death rate of 38.1 per cent in 181 untreated patients in whom a blood culture was not taken.

COMPOSITE TEMPERATURE CURVES

In order to measure in some way the clinical effect of serum in type I and type II lobar pneumonia, we have plotted a composite temperature curve of treated patients for comparison with those that did not receive serum. In chart 6, treated type I patients admitted during the first, second or third day of the disease are compared with untreated patients. (Only patients that recovered are included.) The treated cases are represented by a solid line, the control cases by a dotted line. Each point on these composite temperature curves represents the average temperature for the entire group at that particular stage of the disease. The mean temperature for the treated cases follows a distinctly lower level than the mean temperature of untreated cases from the fourth day of the disease onward. By the sixth day the course for treated cases has reached 100 and it remains at that point or lower, whereas the curve for the untreated cases does not reach 100 until the ninth day.

In chart 7, early type II treated patients who recovered are compared to early type II untreated patients who recovered. These curves differ from the average type I curves in that the two series contain only patients admitted during the first or second day of the disease. A comparison of the type II curves would appear to indicate that specific treatment in type II pneumonia, even when administered early, does not shorten the febrile period. The curves do show, however, that the serum treated patients had a consistently lower fever than did the untreated patients.

In summarizing the clinical effects of concentrated serum, it may be stated that the administration of the serum early in the course of the disease frequently causes a striking drop in the temperature and a general amelioration of the patient's symptoms. In the cases of type I pneumonia treated within three days after onset and type II pneumonia treated within two days after onset, this is the rule rather than the exception. In cases treated later than this, the clinical effect is not always evident. If, however, the particular lot of serum used is highly potent in type I or type II antibodies as the case may be, the clinical effects even in cases admitted on the fourth or fifth day of the disease may be quite impressive. In patients with pneumococci in the blood (type I or type II), the early administration of serum usually causes an immediate disappearance of pneumococci from the blood stream, provided the sepsis is not extreme.

EFFECT OF SERUM TREATMENT ON THE DEATH RATE

As has been pointed out, all the patients with lobar pneumonia included in this series received a number

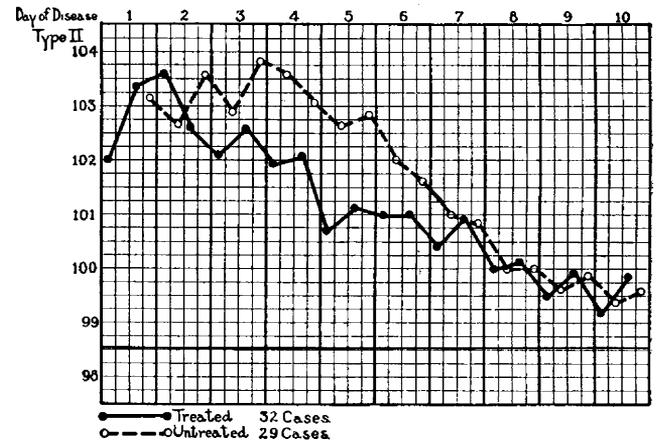


Chart 7.—Mean temperature curve of patients, treated and untreated, admitted during first two days of type II pneumonia.

as soon as the diagnosis of lobar pneumonia was made. Patients with even numbers received serum; those with odd numbers did not receive any. This method of classifying patients left their selection for treatment entirely to chance. The method produced comparative groups that are surprisingly similar in all essential respects. In the first place the number of cases of the treated and untreated types is approximately the same (table 3). Furthermore, the figures have been analyzed with regard to various other factors that might influence the death rate. These factors are: (1) day of admission to the hospital; (2) age; (3) complicating systemic disease, and (4) history of excessive alcoholism. In respect to these factors, chart 8 shows that in the type I and type II groups the distribution of cases in the treated and the untreated series is remarkably similar. In the comparatively small number of type III cases, the treated series contains twice as many instances of systemic disease as the untreated series. The miscellaneous group IV series is less evenly selected than type I and type II in regard to three of the factors: systemic disease, chronic alcoholism and age. Moreover, the irregularities all tend in the same direction; that is, toward the production of a high mortality in the untreated group of cases.

4. Cecil, R. L., and Steffen, G. I.: The Treatment of Experimental Pneumococcus Pneumonia in Monkeys with Pneumococcus Antibody Solution, *Bull. 141, Hyg. Lab., U. S. P. H. S., April, 1925, pp. 18-31.*  
5. Baldwin, H. S.: The Specific Therapy of Pneumococcus Type II Pneumonia, *Am. J. M. Sc. 174: 191-208 (Aug.) 1927.*

The effect of concentrated serum on the death rate in pneumococcus pneumonia is indicated in table 3, which is a summary of the 885 cases of pneumococcus

TABLE 3.—Comparison of Death Rates in Treated and Untreated Cases

Type	Treated			Untreated		
	Cases	Died	Mortality, per Cent	Cases	Died	Mortality, per Cent
I.....	153	32	20.9	147	48	32.6
II.....	106	44	41.5	108	59	54.5
III.....	40	16	40.0	56	16	28.6
IV.....	142	40	28.2	133	51	38.3
	441	132	30.0	444	174	39.2

pneumonia included in the present study. Altogether, 441 patients with pneumococcus pneumonia were classified in the serum treated group.

The most striking results were obtained in the pneumococcus type I series. In 153 treated cases the death rate was 20.6 per cent, while the control series of 147 cases showed a mortality of 32.6

Table 4 is a slight modification of table 3. In table 4, all patients are omitted who died within twenty-four hours after admission to the hospital. Such material seemed hardly suitable for a therapeutic experiment of this kind. The mortality rates show slight differences from those obtained in table 3.

TABLE 4.—Comparison of Death Rates in Treated and Untreated Cases\*

Type	Treated			Untreated		
	Cases	Died	Mortality, per Cent	Cases	Died	Mortality, per Cent
I.....	152	31	20.4	144	45	31.2
II.....	102	40	39.2	102	53	52.0
III.....	38	14	36.8	55	15	27.2
IV.....	137	35	25.5	121	39	32.2
	429	120	28.0	422	152	36.0

\* Patients who died within 24 hours after admission are omitted.

Four factors that produce considerable variation in the death rate of lobar pneumonia have been considered with regard to their distribution in treated and in

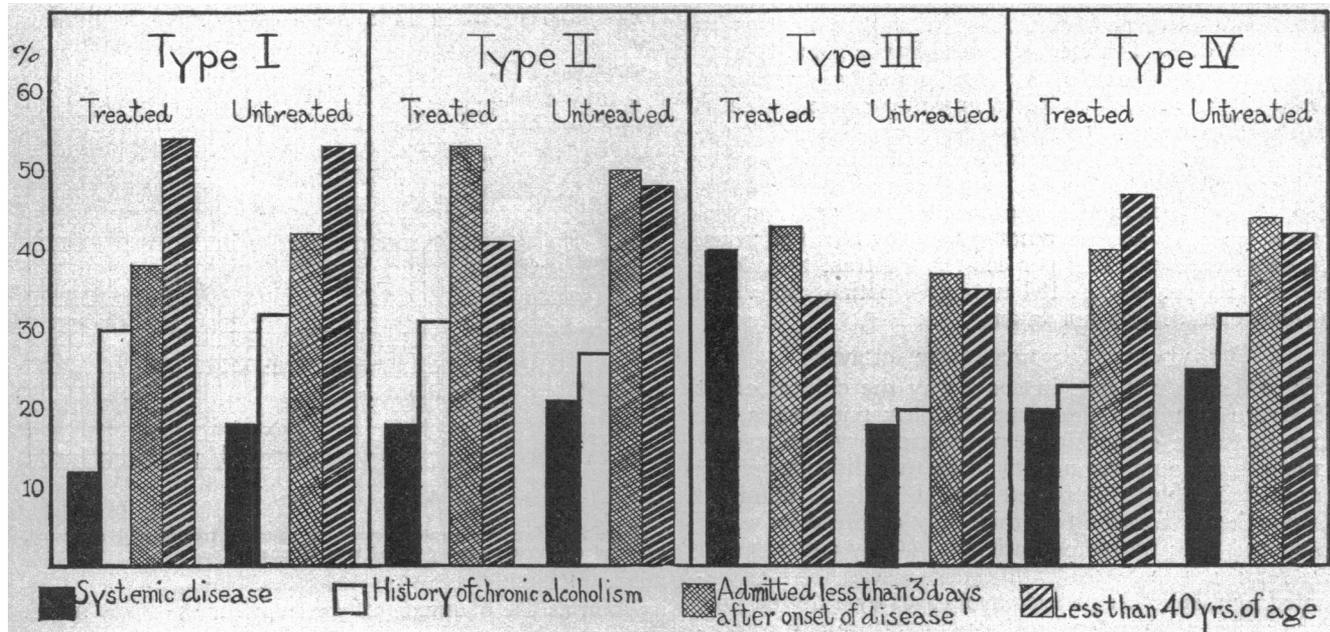


Chart 8.—Distribution of systemic disease, alcoholism, early admissions and age groups in treated and untreated cases.

per cent. Among the pneumococcus type II cases the results were not quite so striking, but even here there was a decided difference in the mortality for treated and untreated cases: 41.5 per cent for the treated series as compared to 54.5 per cent for the untreated cases. In the pneumococcus type III cases, serum did not have any beneficial effect. Indeed, the death rate was actually higher for the treated group (40.0 per cent for the treated, 28.6 per cent for the untreated). This apparent anomaly in the type III mortality rates is probably due, as has been noted, to the presence of an unusually large number of chronically ill patients in the type III treated series. In the miscellaneous group IV cases, serum appears to have had a beneficial effect. In a large group of treated cases the death rate was 28.2 per cent, as compared with 38.3 per cent for the untreated cases. This may also be due, as has been shown, to factors other than serum, which modify the death rate of lobar pneumonia. The death rate for the entire group of 441 treated cases was 30 per cent, while in 444 untreated cases there was a mortality of 39.2 per cent.

untreated cases of this series. The same factors have been considered in relation to the effectiveness of serum therapy. The death rate for untreated patients admitted during the first three days of the disease (table 5) is

TABLE 5.—Treated Cases Admitted During the First Three Days of Disease Compared With Untreated Cases Admitted During the First Three Days of Disease

Type	Treated			Untreated		
	Cases	Died	Mortality, per Cent	Cases	Died	Mortality, per Cent
I.....	60	7	11.7	59	16	27.1
II.....	52	18	34.6	47	19	40.4
III.....	16	6	37.5	19	3	15.8
IV.....	53	12	22.6	51	12	23.5
	181	43	23.7	176	50	28.4

considerably lower than the death rate for untreated patients admitted after the first three days of the disease (table 6). Treated patients admitted during the first three days of the disease (table 5) show a considerably lower death rate than treated patients admitted after the first three days of the disease

(table 6), type III excepted, as it is throughout this discussion. By comparing the statistics in table 5 with those in table 3, it will be seen that the death rates for treated patients admitted during the first three days of the disease are distinctly lower than those for the entire treated series. This is most marked in the type I group, in which the death rate for treated patients admitted early is approximately one half of that for the entire group of treated type I cases. It is also interesting to note that the death rate for treated patients with type II pneumonia admitted early was only 34.6 per cent, as compared with a death rate of 54.6 per cent for the entire group of untreated type II cases. In other words, it would appear from these figures that if patients with type I and type II pneumonia were admitted early and treated early with serum, the death rate for type I pneumonia could be cut to one third of the present figure, and that for type II to almost one half of the present figure.

TABLE 6.—Treated Cases Admitted After the First Three Days of Disease Compared With Untreated Cases Admitted After the First Three Days of Disease

Type	Treated			Untreated		
	Cases	Died	Mortality, per Cent	Cases	Died	Mortality, per Cent
I.....	88	20	22.7	81	28	34.6
II.....	47	20	42.5	50	30	60.0
III.....	21	7	33.3	32	9	28.1
IV.....	80	19	23.7	64	23	35.9
	236	66	27.9	227	90	39.6

The death rate in all four groups of cases, in both the treated and the untreated series, is lower for patients under 40 years of age than for patients over 40 years of age. Relatively speaking, however, serum treatment appears to be just about as effective in middle-aged and elderly patients as it is in younger patients. Statistics were also prepared to determine how effective serum treatment was in patients with chronic systemic disease or with a history of chronic alcoholism. These figures were very similar to those for the two age groups; that is, the death rates in both treated and untreated groups were lower for those with previous good health than for those with a history of systemic disease or chronic alcoholism. The relative reduction in death rate, however, was approximately the same for the chronically ill as for those who had always enjoyed good health.

COMPLICATIONS

The pneumococcus complications, such as empyema, meningitis, endocarditis, pericarditis, arthritis and otitis, occurred about as frequently in the treated as in the untreated series. Apparently the serum treatment of pneumonia has very little effect in reducing the incidence of complications.

COMMENT

It seems safe to conclude from this study that refined and concentrated serum fulfils the requisites of an efficient specific agent.

1. It saves monkeys that have been infected with a lethal pneumococcus pneumonia and septicemia.
2. It usually produces a definite, sometimes striking clinical effect on patients with pneumococcus type I pneumonia when they are treated during the first three days of the disease, and on patients with type II pneumonia when they are treated during the first two days of the disease.
3. In a large group of treated patients checked by alternate untreated controls, concentrated serum has

reduced the death rate one third in type I and one fourth in type II pneumonia. In the miscellaneous group IV, the death rate in treated patients appears to have been reduced one fifth, but this difference might possibly be explained by some other factor, such as the unequal distribution of systemic disease, chronic alcoholism and old age. In the small type III series, analysis of the figures reveals that a large number of the treated cases were complicated by systemic diseases. This makes it impossible to compare these cases, and they are included in the various tables only for the sake of completeness.

It is fortunate that Felton has been able to produce a refined derivative of antipneumococcus serum which can be injected intravenously in adequate amounts without producing thermal reactions. As a matter of fact, a few of the lots that have been used at Bellevue Hospital were found to be chill-producing and their use was immediately discontinued. Though some inequality still exists in the potency of various lots of concentrated serum, this is a difficulty that can be overcome by regulating the dosage in cubic centimeters to meet the potency of the serum in units. The impression was gained that the best clinical results were obtained when daily doses of 100,000 units or more were given early in the course of the disease.

The question of dosage has been studied from the experimental standpoint by Park and Cooper.<sup>6</sup> They advise the establishment of a "balance of protection," to be measured by the mouse protection test and performed with the patient's blood serum. They recommend on the basis of their experiments that in the average case an effort should be made to administer 10,000 units in 5 or 10 cc. of concentrated serum three times a day, thereby helping those patients that may be helped and avoiding waste of the patient's and the state's money in expensive serum production.

Our own experience in Bellevue Hospital has inclined us to the belief that in general relatively large doses of serum have yielded better results than small doses. It appears from a survey of treated cases in the present series that the best results have been associated with maximum doses of serum. This is especially true in the production of sharp crises and striking clinical effects. These have resulted with regularity only when our program was meticulously carried out and the highest number of units was given. It must be admitted, however, that treatment with large doses is expensive and for this reason may prove economically unpractical.

What are the indications for the serum treatment of pneumonia? Provided a concentrated polyvalent anti-serum such as that used in this study is available, serum treatment would appear to be indicated in practically all cases of type I and type II pneumonia. Whether serum treatment should be instituted before the pneumococcus type has been determined is a debatable question. In order to save valuable time, however, our own inclination would be to administer serum promptly in patients with frank lobar pneumonia as soon as the clinical diagnosis has been made. If the sputum shows type I or type II pneumococcus, serum treatment should be continued. If the case proves to be a type III or one of the miscellaneous group IV infections, serum treatment should be discontinued. In both hospital and private practice, the question will arise whether serum treatment should be administered late in the disease. Although clinical and experimental evidence would indi-

6. Park, W. H., and Cooper, Georgia: Antipneumococcus Serum in Lobar Pneumonia: Administration and Dosage, J. A. M. A. 90: 1354-1358 (April 28) 1928.

cate that in pneumonia, as in other acute infections, serum treatment is most effective when begun early, there is evidence from the present study that serum treatment is not without value in later cases of type I and type II pneumonia.

What are the contraindications to serum treatment in pneumonia? At the present time there is no evidence to support the use of serum in type III or group IV pneumonia. In asthmatic patients or in patients who have previously received large amounts of horse serum, it is doubtful whether serum treatment should be employed at all. In patients who give a positive skin reaction, serum should be administered with the greatest caution. Only a small percentage of such patients, however, will give an allergic reaction after the injection of serum. A positive ophthalmic reaction to diluted horse serum is a definite contraindication to serum therapy. It is doubtful whether serum should be administered intravenously to patients suffering with cardiac decompensation, though several such patients have been treated in the present series without untoward effects.

Investigation of the therapeutic value of concentrated serum has not been confined to Bellevue Hospital. A carefully controlled series of cases of lobar pneumonia has been studied in the Harlem Hospital, and the results were recently reported by Bullowa.<sup>7</sup> Bullowa's figures are quite similar to those submitted here and tend to corroborate our conclusion that concentrated serum is of definite value in type I and type II pneumonia. Concentrated serum has also been used at the New York Hospital and at the Boston City Hospital. The results obtained at these two institutions will no doubt be reported in the near future.

#### SUMMARY

1. Refined antipneumococcus serum is a purified and concentrated derivative of ordinary antipneumococcus horse serum. It is usually prepared in a polyvalent form, containing immune bodies against pneumococcus types I, II and III. Its potency against type I and type II is quite high. Its potency against type III is insignificant.

2. Concentrated serum, when injected intravenously into monkeys infected with lethal doses of pneumococcus type I, promptly sterilizes the blood and causes a rapid resolution of the pneumonic exudate.

3. When concentrated serum is injected intravenously into patients in the early stages of pneumococcus type I pneumonia, a striking clinical effect is usually obtained. The bacteria disappear from the blood and the temperature falls rapidly to normal. Even in late cases, good results are often obtained. In type II pneumonia the clinical results are not so impressive, though here again in patients treated early, favorable results are often noted. In type III pneumonia, no clinical effect has been observed. In type IV pneumonia the beneficial effect of serum is questionable.

4. In 441 cases of lobar pneumonia treated with refined polyvalent serum, the death rate was 30 per cent. In a control series of 444 cases, the death rate was 39.2 per cent. In respect to the death rate, the refined serum produced its most striking effect in pneumococcus type I pneumonia. In a series of 153 treated type I cases the death rate was 20.9 per cent, while a control series of 147 untreated type I cases showed a death rate of 32.6 per cent. A definite but less marked

effect on the death rate was observed in cases of pneumococcus type II pneumonia that were treated with concentrated serum. The serum had no favorable effect on the death rate in pneumococcus type III pneumonia. In type IV pneumonia the death rate was lower in the treated than in the untreated series, but factors other than serum may have been responsible for this difference.

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#### MENTAL DISEASE AND THE INDUCTION OF ABORTION\*

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EDITORIAL NOTE.—This paper, together with the paper by Drs. Mussey and Keith, concludes the symposium on pregnancy. In our last issue we published the papers of Dr. Gardiner, and Drs. Hamilton and Kellogg.

Every now and then the question arises whether a pregnancy should be terminated because of the existence of mental disease in the prospective mother or because with preceding pregnancies there have been attacks of mental disorder. The question is sometimes raised also because of a fear that the offspring will be abnormal mentally. In this article it is my purpose to discuss the relations between pregnancy and mental disease in the light of personal experience and of modern views concerning the etiology of mental diseases. Since the data are of a negative character it will follow necessarily that the opinions expressed are somewhat dogmatic.

A survey of the literature reveals little that has been written directly on this topic. The most important contributions that I have been able to find are the outcome of a symposium<sup>1</sup> at a meeting of the Section of Obstetrics and Gynecology of the British Medical Association at Nottingham in 1926; this led to a joint meeting between the Medicolegal Society and the Section of Obstetrics and Gynecology of the Royal Society of Medicine, Jan. 21, 1927. The subject has been admirably discussed in an article by Dr. Percy Smith<sup>2</sup> of London.

Under the heading of mental diseases, popularly called insanity, are included conditions that are fundamentally disorders in the manner in which a person meets the conditions surrounding him. Their causation is consequently complex; it includes factors that depend on the bodily constitution, both as inherited and as modified by life experience—in which is included disease and other injury—and others that belong to the facts to be faced in the world outside the man himself. It is often impossible to differentiate actually between these two groups of factors, which may be and usually are operative at the same time. This may be expressed by saying that the causes are both direct and indirect, the former being mainly conditions within the man himself and the latter precipitating causes, which are most often to be found in the circumstances surrounding him.

Among mental diseases, then, one can recognize two large groups: (1) those that are directly due to disturbance of brain function from disease somewhere in the body; for example, the states of delirium and confu-

\* Read before the Section on Obstetrics, Gynecology and Abdominal Surgery at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, June 14, 1928.

1. Eden, T. W.: Indications for the Induction of Abortion, *Brit. M. J.* 2: 239 (Aug. 7) 1926. Cole, R. H.: The Plea of Insanity, *ibid.*, p. 244; Report of Joint Meeting of Medicolegal Society and the Section of Obstetrics and Gynecology of the Royal Society of Medicine, *ibid.* 1: 188 (Jan. 29) 1927. Lord, J. R.: The Induction of Abortion in the Treatment and Prophylaxis of Mental Disorder, *J. Ment. Sc.* 73: 390 (July) 1927.  
2. Smith, Percy: *Brit. M. J.* 1: 1 (Jan. 7) 1928.

7. Bullowa, J. G. M.: The Use of Pneumococccic Refined Serum in Lobar Pneumonia, *J. A. M. A.* 90: 1349-1351 (April 28) 1928.