The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 95, No. 21 CHICAGO, ILLINOIS NOVEMBER 22, 1930

PNEUMOCOCCUS TYPE I PNEUMONIA

A STUDY OF ELEVEN HUNDRED AND SIXTY-ONE CASES, WITH ESPECIAL REFERENCE TO SPECIFIC THERAPY *

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The classification of pneumococci into specific biologic groups has transformed the medical point of view with respect to pneumonia. Formerly, the physician asked: "Is it lobar or bronchopneumonia?" Today, he asks, "Is it type I, type II or type III pneumonia?" This change in attitude is fitting and proper, for the etiology of a disease is of much greater practical significance than its anatomic characteristics. Furthermore, recent studies in this field have shown that the three dominant types of pneumococci are not only biologically specific but, in addition, produce more or less characteristic clinical pictures.

PNEUMOCOCCUS TYPE I PNEUMONIA

For the past ten years all cases of lobar pneumonia admitted to the medical wards of Bellevue Hospital have received careful bacteriologic study. During this time, 1,161 cases of pneumococcus type I pneumonia have come under our observation. In the present paper we subject this series of cases to clinical analysis and report the results of specific therapy. This series includes thirty cases of type I pneumonia which have occurred in children.

Method of Typing.—The mouse method was used as a routine in the bacteriologic examination of sputum. Agglutination and precipitin tests were performed with the peritoneal exudate of the mouse, and at the same time cultures were taken on blood-agar plates from both the heart's blood and peritoneum of the mouse. In fatal cases that came to autopsy, intravitam cultures were controlled by postmortem cultures. During the past two years, Sabin's [1] rapid method of typing has been extensively employed and has often made it possible to determine the pneumococcus type on the same day the patient was admitted to the hospital. In addition to the routine sputum cultures, many patients were subjected to blood cultures, and cultures were made from all pleural, pericardial and joint exudates.

Incidence.—Although pneumococcus type I is rarely found in healthy throats, type I pneumonia is the most prevalent of all the types. This fact is well brought out in table 1, in which the incidence of types in the adult series is listed. Of 3,662 cases of lobar pneumonia in adults, 1,131, or 30.9 per cent, were type I infections; type II was next in frequency, with an incidence of 23.2 per cent; type III caused only 11.9 per cent. The miscellaneous group of pneumococci was responsible for 34.1 per cent of the pneumonias studied in this series; however, a recent classification of this group into its component types shows that none of the twenty-three new types described by Park and Cooper [2] compare in frequency with pneumococcus type I as an exciting agent of pneumonia in adults.

Pneumococcus type I pneumonia is, therefore, the commonest form of lobar pneumonia, constituting almost one third of all the lobar pneumonias in Bellevue Hospital. The Bellevue figures agree closely with those of other institutions. For example, in Cole's [3] series of cases, 33.3 per cent were type I infections; in the series of Park, Bullowa and Rosenbluth,[4] 28.5 per cent were of this type.

Occurrence in Children.—It is interesting to compare the incidence of pneumococcus type I in adults with that in children. In a bacteriologic study of 147 cases of pneumonia in children, Plummer, Raia and Shultz [5] encountered only 14 type I infections, or 9.5 per cent. All but three of these occurred after the third year. From these figures it appears that type I pneumonia is quite rare in infants, while in children between the ages of 3 and 12 years it constitutes only 10 per cent of the total group.

Incidence According to Age.—In an analysis of 2,000 cases of pneumonia reported in 1927, Cecil, Baldwin and Larsen [6] pointed out that pneumococcus type I pneumonia was essentially the pneumonia of young people. In 585 cases of lobar pneumonia occurring in adults under 30 years of age, these investigators found that 246, or 42 per cent, were type I infections. In the present series of 1,127 type I pneumonias, 696, or 61.8 per cent, occurred in individuals between 10 and 40 years of age.

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

* Read before the Section on Pharmacology and Therapeutics at the Eighty-First Annual Session of the American Medical Association, Detroit, June 27, 1930.

* Because of lack of space, this article is abbreviated in THE JOURNAL. The complete article appears in the Transactions of the Section and in the authors' reprints.

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1. Sabin, A. B.: The "Stained Slide" Microscopic Agglutination Test: Application to (1) Rapid Typing of Pneumococci; (2) Determination of Antibody, Proc. Soc. Exper. Biol. & Med. **26:** 492-494 (March) 1929.

2. Cooper, Georgia; Edwards, Marguerite; and Rosenstein, Carolyn: The Separation of Types Among the Pneumococci Hitherto Called Group IV and the Development of Therapeutic Antiserums for These Types, J. Exper. Med. **49:** 461-474 (March) 1929.

3. Avery, O. T.; Chickering, H. T.; Cole, Rufus; and Dochez, A. R.: Acute Lobar Pneumonia; Prevention and Serum Treatment, Monograph 7, Rockefeller Institute for Medical Research, Oct. 16, 1917.

4. Park, W. H.; Bullowa, J. G. M., and Rosenbluth, M. B.: The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, J. A. M. A. **91:** 1503-1507 (Nov. 17) 1928.

5. Plummer, Norman; Raia, Antoinette; and Shultz, Selma: Pneumonia in Children, Am. J. Dis. Child. **40:** 557-568 (Sept.) 1930.

6. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Lobar Pneumonia; A Clinical and Bacteriologic Study of Two Thousand Typed Cases, Arch. Int. Med. **40:** 253-280 (Sept.) 1927.

Clinical Features.—Pneumococcus type I pneumonia might perhaps be called the prototype of lobar pneumonia. With few exceptions, the type I patient gives a typical history, presents the typical signs and symptoms, and has a typical course. In a great majority of the patients, the onset is marked by a chill and pain in the side. The characteristic cough, accompanied by rusty sputum, soon makes its appearance. The temperature is prone to run along on a high plateau between 103 and 105 F., and in a majority of the cases the termination is marked by crisis rather than by lysis.

Complications.—The incidence of serious complications in 1,131 cases of pneumococcus type I pneumonia in adults is given in table 2. Other complications were: pleural effusion, 26 cases; jaundice, 19 cases; delayed resolution, 17 cases; cellulitis, 32 cases, and cardiac irregularity, 26 cases. Pneumothorax developed in 3 patients, lung abscess in 4.

TABLE 1.—*Incidence of Pneumococcus Types in Lobar Pneumonia of Adults Treated in Bellevue Hospital 1920-1930* *

Pneumococcus	Number of Cases	Percentage of Incidence
Type I	1,131	30.9
Type II	850	23.2
Type III	434	11.9
Group IV	1,247	34.1
Total	3,662	

* This series does not include cases admitted during the season of 1925-1926.

The common complications in children were empyema and otitis media. In 30 cases of type I pneumonia in children, empyema was noted in 5, or 16.7 per cent. Otitis media also occurred in 5 patients.

Bacteremia.—From 1926 to 1930, 470 type I patients were subjected to blood cultures and 90, or 19.2 per cent, showed a pneumococcus bacteremia. During the past year, blood cultures have been carried out as a routine procedure in 64 cases; 19 of these yielded pneumococci, an incidence rate of 29.7 per cent. This figure corresponds with that reported by other investigators.

Mortality Rate.—The death rate from pneumococcus type I pneumonia differs considerably in different institutions, depending particularly on the type of patient which the hospital admits to its wards. Figures reported by Wadsworth,[7] Locke,[8] Cole [3] and others show a mortality for patients with type I pneumonia not receiving serum of 15 to 25 per cent. In our Bellevue series

TABLE 2.—*Serious Complications in Pneumococcus Type I Pneumonia*

	Number	Per Cent
Empyema	73	6.5
Meningitis	20	1.8
Acute arthritis	10	0.9
Suppurative pericarditis	7	0.6
Endocarditis	4	0.4
Phlebitis	5	0.5

of 412 cases without serum, in the period from 1920 to 1929, there is a mortality of 28.2 per cent.

The death rate for type I pneumonia in Bellevue Hospital has shown a steady rise since 1921, the second year of our investigation. The annual death rate of patients not receiving serum is given in table 3.

7. Wadsworth, A. B.: Review of Recently Published Reports on the Serum Treatment of Type I Pneumonia, Together with a Report of 445 Additional Cases, Am. J. Hyg. **4**: 119 (March) 1924.
8. Locke, E. A.: The Treatment of Pneumococcus Type I Pneumonia with Specific Serum, J. A. M. A. **80**: 1507 (May 26) 1923.

It is extremely important to note that in the period from 1921 to 1929 the mortality rate has increased from 20 per cent to 42.8 per cent. An explanation of this increase is not entirely clear; however, such factors as the influenza epidemic of 1918 and the increasing incidence of alcoholism seem to be important.

TABLE 3.—*Annual Death Rate of Patients Not Receiving Serum*

Year	Percentage of Mortality
1920-1921	23.8
1921-1922	20.0
1924-1925	26.4
1926-1927	30.4
1927-1928	35.3
1928-1929	42.8

Table 4 presents the comparative death rates in the Hospital of the Rockefeller Institute [9] and in Bellevue Hospital. From this table it is evident that the death rate at Bellevue Hospital for lobar pneumonia (all types) is almost twice that of the Rockefeller Hospital. The reason for this difference is not entirely clear. Probably the most important factor is the difference in type of patient admitted. Other possible factors are incidence of alcoholic patients, character of nursing, amount of examination by students, and frequency of oxygen therapy.

The mortality rate for type I pneumonia in our series varied, of course, with the age of the patients. In children under 12 years of age it was 3.3 per cent; the figures rose with each decade until in patients over 50 it was 46.2 per cent.

The death rate for type I pneumonia was greatly affected by the presence of pneumococcus bacteremia.

TABLE 4.—*Comparative Death Rates in Hospital of Rockefeller Institute and in Bellevue*

	Rockefeller Hospital[9]	Bellevue Hospital
Type I	11.6*	28.2†
Type II	28.5	48.9
Type III	43.0	34.1
Group IV	12.8	31.3
Total series	19.5	34.5

* Mostly serum treated cases.
† None received serum.

For example, in our series there were 412 patients with type I pneumonia who received no serum. Of these, 45 patients who showed a pneumococcus bacteremia had a death rate of 66.7 per cent, while 80 type I patients with negative blood cultures showed a death rate of only 22.5 per cent. In other words, the death rate was three times as high in the septic cases as in the nonseptic cases in this group.

The death rate in patients with serious complications was very high. Twenty-nine cases of pneumococcus type I empyema showed a death rate of 51.7 per cent. This figure, however, is a little misleading, owing to the frequent discovery of pus in the pleura of moribund patients admitted late in the disease. Five patients with suppurative pericarditis, two with vegetative endocarditis, and eleven with meningitis all died.

Specific Treatment.—The studies of Neufeld [10] in Germany and of Cole [3] in America (1913) mark the beginning of the modern specific therapy of pneumonia.

9. Cole, R. I.: Acute Pulmonary Infections, De Lamar Lectures, 1927-28, Baltimore, Williams & Wilkins Company, 1928.
10. Neufeld, F., and Händel, L.: Arb. a. d. k. Gsndhtsamte **34**: 293, 1910.

In Cole's investigations, horses were highly immunized against type I pneumococci; the serum of these horses was then injected intravenously into patients infected with type I pneumonia. The doses of serum recommended were quite high, 100 cc. intravenously every eight hours until the temperature dropped and the patient showed definite improvement. Cole,[11] in a recent review of his studies on the serum treatment of type I pneumonia, gives a complete description of the work. In Cole's series of 431 cases of type I pneumonia, practically all the patients received type I serum. The death rate for his entire series was 10.2 per cent, but there was no control series for comparison.

EVIDENCE OF VALUE OF TYPE I PNEUMOCOCCUS SERUM

Since the original studies of Cole, Dochez and others [3] on the value of type I antipneumococcus serum, a considerable amount of evidence in favor of the value of type I serum has accumulated from various sources. For convenience, this evidence can be submitted under three headings: (1) experimental; (2) clinical; (3) statistical.

1. *Experimental Evidence.*—The experimental evidence in favor of type I serum is very convincing. In the first place, the serum of a horse immunized against pneumococcus type I contains the same immune bodies (agglutinins, precipitins and protective substance) that are found in the human blood of the pneumonic patient after crisis. Furthermore, when a mouse is given as many as a million fatal doses of pneumococcus culture, its life can be saved by the prompt injection of an adequate amount of type I antipneumococcus serum.

Cecil and Blake found that, in the experimental pnuemococcus type I pneumonia of monkeys, type I serum, in every case, saved the animals that had been injected intratracheally with lethal doses of type I pneumococcus culture. Normal horse serum had no therapeutic effect on the infected monkeys.

Goodner [12] has recently contributed additional evidence of the value of type I serum in experimental pneumococcus infections in rabbits, produced by intracutaneous injection of the organisms. Rabbits that received lethal doses of pneumococcus type I intracutaneously were readily saved by intravenous injections of type I serum.

The experimental evidence, therefore, is decidedly in favor of the therapeutic value of type I serum.

2. *Clinical Evidence.*—Cole [3] first pointed out the striking clinical effect that frequently follows the intravenous injection of type I serum. Within twenty-four hours the temperature, together with the pulse and respiratory rate, often drops from a high point to normal. Toxic symptoms are ameliorated and the patient's whole appearance changes. Perhaps the most significant of all the clinical effects is the prompt disappearance of pneumococci from the blood stream of septic patients.

These observations of Cole have been abundantly confirmed by other investigators. It must be admitted that such a prompt and striking clinical effect is not observed in every case and that the patients most likely to yield satisfactory results are those who receive serum early in the disease.

3. *Statistical Evidence.*—The statistical evidence in favor of type I serum is not so convincing as one would expect from the experimental and clinical evidence in its favor. Cole treated 431 cases of type I pneumonia with type I serum and reported a death rate of only 10.2 per cent. As no control series was studied, however, it is impossible to say what the death rate would have been if no serum had been used.

Locke [8] and, more recently, Wadsworth [7] have published their results on the treatment of type I pneumonia with type I serum, the two investigators obtaining the same death rate (from 17 to 18 per cent). In both series, however, patients who were not given serum showed approximately the same death rate (from 17 to 19 per cent).

INVESTIGATIONS AT BELLEVUE HOSPITAL

In 1920 we initiated our studies on the specific treatment of lobar pneumonia at Bellevue Hospital. At this time, standard type I serum had been in use for seven years. On account of certain practical difficulties, it had not achieved the popularity which it apparently deserved. The serum was beneficial for only one type of pneumonia; not infrequently, it excited sharp reactions, either allergic or thermal in the patient; and, further, the technical difficulties connected with the administration of large intravenous doses of serum militated strongly against the extensive use of the serum in small hospitals and in private practice. Even in many large metropolitan hospitals type I serum had been completely abandoned when the studies on refined antipneumococcus serums at Bellevue Hospital were initiated. The time seemed appropriate for testing the therapeutic effect of various serum derivatives with the hope of ultimately obtaining a refined and concentrated product that would be easy to administer, free from untoward after-effects, and possibly polyvalent in character.

HUNTOON'S ANTIBODY SOLUTION

For two years, our attention was concentrated on Huntoon's antibody solution, a water clear solution of antipneumococcal immune bodies, polyvalent for types I, II and III. This product has a very low nitrogen content, and the amount of horse serum protein is so minute that it cannot be detected by chemical tests.

Huntoon's antibody solution contains a high content of protection against pneumococcus type I, 0.2 cc. usually protecting a mouse against 0.1 cc. of a virulent culture. Its protective power against type II is not so marked, while against type III its potency is even lower, the best lots rarely protecting against more than 0.001 cc. of virulent type III culture. The results of our two years' experience with Huntoon's antibody solution [13] have been published in full. At this time it will suffice to refer only to the results obtained in the treatment of type I pneumonia. The actual figures are shown in table 5. One hundred and seventy-one cases of type I pneumonia admitted to six medical wards were treated with antibody solution and showed a death rate of 14 per cent; 171 control cases admitted to six other medical wards during the same period of time received no specific treatment and showed a death rate of 21.1 per cent. In 56 cases of type I pneumonia admitted within forty-eight hours after onset of the disease, treatment with the antibody solution yielded a death rate of only 8.9 per cent, whereas 68 control

11. Cole, Rufus: Serum Treatment in Type I Lobar Pneumonia, J. A. M. A. **93**: 741-747 (Sept. 7) 1929.
12. Goodner, Kenneth: Further Experiments with the Intradermal Pneumococcus Infection in Rabbits, J. Exper. Med. **48**: 413-429 (Sept. 1) 1928.
13. Cecil, R. L., and Larsen, N. P.: Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia, with Special Reference to the Therapeutic Value of Pneumococcus Antibody Solution: Preliminary Report, J. A. M. A. **79**: 343-348 (July 29) 1922.

cases admitted to the control wards within forty-eight hours of onset showed a death rate of 23.5 per cent, almost three times that for the treated cases.

Huntoon's antibody solution gave very good clinical results and did away with one of the disadvantages of type I serum; it was never followed by anaphylactic reactions or serum sickness. It, however, possessed no more potency than standard type I serum, and large doses of from 50 to 100 cc. were necessary for satisfactory results. When injected intravenously, the antibody solution produced chills much more frequently than type I serum. Indeed, during the early days of our work with this product, almost every intravenous injection of the solution was followed by a sharp chill and rise of temperature. These thermal reactions were sometimes quite severe, and in three cases the intravenous injection of antibody solution appeared to be the immediate cause of death.

Summarizing, Huntoon's antibody solution was free from horse protein but was no more concentrated than the original type I serum. It yielded very good clinical and statistical results in type I pneumonia, but the injections were often followed by severe thermal reactions.

TABLE 5.—*Comparison of Mortality Rates in Cases Treated with Huntoon's Antibody Solution and Control Cases* *

	Treated			Control		
Year	Cases	Deaths	Mortality, per Cent	Cases	Deaths	Mortality, per Cent
1920-1921	87	14	16.1	79	18	22.8
1921-1922	84	10	11.9	92	18	19.6
Total.....	171	24	14.0	171	36	21.1

* Patients who died within twenty-four hours of admission are not included.

FELTON'S CONCENTRATED SERUM

From 1924 to 1929, alternate cases of pneumococcus type I pneumonia have been treated in Bellevue Hospital with Felton's concentrated antipneumococcus serum.

Felton's antipneumococcus serum is prepared as follows:

> Twenty per cent anhydrous sodium sulphate is added to standard antipneumococcus serum and allowed to stand in an incubator at 37 C. from one to two hours until a precipitate forms. After filtration the precipitate is dialized in running water from five to seven days, viscous membranes being used for the dialysis. The content of the sac is then adjusted to a p_H of from 4.6 to 4.8, at which point a second precipitate forms. This precipitate is removed and the clear supernatant fluid containing immune bodies and some globulin and albumin is adjusted to a p_H of 6.8 and diluted four or five times with cold distilled water. A white precipitate is thrown down containing practically all the protective substance in the original serum. This precipitin dissolves readily in sodium chloride, is high in protective power, and is practically free from chill-producing substances.[14]

The concentration of Felton's serum varies somewhat with different lots; this inequality, however, is readily overcome by pooling the serums from several horses. The actual ratio of its potency to unconcentrated serum has been difficult to determine for the reason that laboratories have employed different methods of standardization. Felton[15] has recently published an article on the concentration of antipneumococcus serum in which he presents comparisons of the common immunologic reactions of unconcentrated serum with those of concentrated serum. The figures are so impressive that the table is reproduced in full (table 6).

TABLE 6.—*Comparison of the Common Immunologic Reactions of Pneumococcus Serum and Its Concentrate (Felton)* [15]

	Type I Serum	Type I Concentrate
Precipitins.....	25-50*	100-900
Agglutinins.....	10	100
Complement fixation.....	10	100
Opsonins.....	40	360
Bactericidal action †.....	10^3	2×10^6
Protection.....	500	7,000
Neutralization.....	50	500

* Numbers indicate highest dilutions giving positive reactions.
† Numbers indicate actual number of bacteria killed.

In this experiment the concentrate was prepared from a certain lot of standard serum and then compared with the original serum in respect to its content of immune bodies. From the results shown in the table, there can be no doubt that the concentrate represents a real concentration of all the known antibodies of antipneumococcus serum. In this particular experiment the immune bodies in the concentrate averaged about ten times the potency of those in the original serum.

Two methods have been employed for testing the potency of antipneumococcus serum. In the older method, recommended by Cole and adopted by the United States Hygienic Laboratory, mice are injected with a constant dose of serum and a varying amount of pneumococcus culture. In Felton's method, the mice receive a constant amount of culture and varying dilutions of serum. The Hygienic Laboratory test requires the survival of 50 per cent of the mice injected simultaneously with 0.2 cc. of serum and 0.1 cc. of an eighteen-hour broth culture of pneumococcus of such virulence that 0.00000001 cc. causes death. The "unit of protection" that Felton employs is that amount of serum which will protect mice against one million lethal doses of virulent pneumococci. According to Felton's "unit" method, a wide variation in potency, ranging from 100 to 2,000 units per cubic centimeter can be demonstrated in serums that have already passed the Hygienic Laboratory standard. In other words,

TABLE 7.—*Mouse Protection Test on Antipneumococcus Serums (Hygienic Laboratory Method)*

Amount of Serum	Gov. Standard No. P. 8.	N. Y. State No. 406	Felton's Conc. No. 62
0.2 cc. undiluted.....	S*	S*	D*
0.2 cc. 1:5.....	D	S	S
0.2 cc. 1:10.....	D	S	S
0.2 cc. 1:20.....	D	D	S
0.2 cc. 1:40.....	—	D	S
0.2 cc. 1:80.....	—	—	S

* One-tenth cubic centimeter virulent broth culture in every case. S signifies that two out of three mice inoculated survived, and D, that two out of three died.

the Hygienic Laboratory test is one that sets a minimum standard of potency but does not measure the extent by which the serum may exceed the standard in protective value.

In Cole's recent article on the serum treatment of type I pneumonia, he questions the accuracy of Felton's method of standardization and contends that the only reliable method of testing potency is to subject the serum to the most rigorous test possible, namely, that

14. Felton, L. D.: Concentration of Pneumococcus Antibody, J. Infect. Dis. **43**: 543-553 (Dec.) 1928.
15. Felton, L. D.: The Concentration of Antipneumococcus Serum, J. A. M. A. **94**: 1893-1896 (June 14) 1930.

0.1 cc. or 0.2 cc. of the serum shall protect a mouse against 0.1 cc. of a culture of the highest virulence. He suggests that the simplest and most satisfactory way to test concentrated serum would be to make various dilutions of it and test them in the same manner that the whole serum is tested. We have actually carried out such a test and the results are shown in Table 7.

Various dilutions of government standard serum, New York State serum, and Felton's concentrated serum were tested for protective power in mice, each mouse receiving 0.2 cc. of serum and 0.1 cc. of virulent broth culture. When tested by this method the concentrated serum was found to have protective power in much higher dilutions than the unconcentrated preparations. With Felton's serum the mice survived at a dilution of 1:80. With the New York State serum a dilution of 1:10 was the highest to protect mice, and with the government standard serum only the undiluted preparation gave protection. The failure of the undiluted concentrated serum to protect mice is explained on the basis of the well known "zone phenomenon," which so frequently occurs in immunologic reactions.

In Goodner's interesting study of the therapeutic value of various antipneumococcic serums in experimental pneumococcus infection of rabbits, he found

TABLE 8.—*Comparison of Agglutinin and Rabbit Therapeutic Value of Unconcentrated and Concentrated Serums (Goodner)*

Serum Number	Rabbit Therapeutic Value (Minimal Effective Dose of Serum)	Agglutinin Titer
1. Antipneumococcic serum (horse). Hygienic Laboratory Control P 7	3.0	80
2. Antipneumococcic serum (horse). Massachusetts Antitoxin and Vaccine Laboratory, Lot P 315	3.5	40
3. Concentrated pneumococcus antibodies (Felton). Type I, Lot 56	0.2	640

that the minimal effective dose was much smaller for Felton's serum than for unconcentrated preparations. Table 8 is part of one of Goodner's [12] protocols and is reproduced here because it shows so clearly the relative therapeutic value of concentrated and unconcentrated serums. The minimal effective dose of Felton's serum (0.2 cc.) was approximately one fifteenth of the minimal effective dose of either of the two unconcentrated preparations. The difference in agglutinin titer was even more marked.

At the outset of our work we tested the therapeutic value of Felton's serum on monkeys experimentally infected with pneumococcus type I pneumonia. Four monkeys were given lethal doses of pneumococcus type I intratracheally and all four animals promptly developed pneumonia and pneumococcus bacteremia. Twenty-four hours after infection, three of the monkeys each received several intravenous injections (from 5 to 10 cc.) of concentrated serum. The three treated monkeys showed almost immediate signs of improvement, and pneumococci disappeared from the blood stream. The fourth monkey did not receive any serum and died on the third day with a heavy pneumococcal septicemia.

In our investigations with Felton's serum the alternate case method was used; that is, every patient diagnosed as having lobar pneumonia was given a number; the patients with even numbers received the serum—those with odd numbers served as controls. The method of administering the concentrated serum has been described in detail in a previous article.[16] After a preliminary test for sensitiveness to horse serum, 5 cc. of concentrated serum was slowly injected intravenously. From one to two hours later, from 10 to 20 cc. was

TABLE 9.—*Comparison of Mortality Rates in Cases Treated with Felton's Concentrated Serum and Control Cases* *

Year	Treated: Cases	Treated: Deaths	Treated: Mortality, per Cent	Control: Cases	Control: Deaths	Control: Mortality, per Cent
1924-1925	49	10	20.4	57	15	26.3
1926-1927	68	12	17.7	77	22	28.6
1927-1928	88	19	22.9	67	23	34.3
1928-1929	39	7	18.0	33	13	39.4
Total.....	239	48	20.1	234	73	31.2

* Patients who died within twenty-four hours of admission are not included.

given intravenously, the dose depending on the potency of the lot and the severity of the case. In general, we have tried to administer from 100,000 to 200,000 units (from 40 to 100 cc.) during the first twenty-four hours of treatment. It is our present conviction that in most cases serum treatment should be completed in forty-eight hours; that is, if results are to be obtained at all, they will usually be obtained within that time.

Clinical Effect.—There is no more striking clinical effect in the whole domain of specific therapy than that which frequently follows the early administration of Felton's serum in type I pneumonia. The temperature drops rapidly, very much as in a natural crisis, and all signs of toxemia frequently disappear within twenty-four hours after the initiation of treatment.

The effect of concentrated serum on pneumococcal septicemia is quite as marked as that of unconcentrated serum. Unless the sepsis is extreme (several hundred colonies to 1 cc. of blood), pneumococci disappear from the blood stream after one or two injections of serum.

Effect on the Mortality Rate.—The effect of concentrated serum on the mortality rate of type I pneumonia is indicated by year in table 9. All together, 239 cases of type I pneumonia have been treated with

TABLE 10.—*Comparison of Mortality Rates in Cases Treated with Felton's Concentrated Serum and Control Cases Admitted Within Seventy-Two Hours of Onset* *

Year	Treated: Cases	Treated: Deaths	Treated: Mortality, per Cent	Control: Cases	Control: Deaths	Control: Mortality, per Cent
1924-1925	26	2	7.7	25	7	28.0
1926-1927	22	0	0.0	27	4	14.8
1927-1928	33	6	18.2	28	9	32.1
1928-1929	22	4	18.2	17	6	35.3
Total.....	103	12	11.7	97	26	26.8

* Patients who died within twenty-four hours of admission are not included.

Felton's concentrated serum, with a death rate of 20.1 per cent; 234 alternate controls show a death rate of 31.2 per cent. It is noteworthy that, in the four year period, the death rate of the treated cases has varied from 17.7 to 22.9 per cent, and for the controls from 26.3 to 39.4 per cent. Table 10 is a comparison of mortality rates in cases admitted within seventy-

16. Cecil, R. L., and Sutliff, W. D.: The Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, J. A. M. A. **91**: 2035-2042 (Dec. 29) 1928.

two hours of onset of symptoms. Here the contrast between the death rate in treated and control cases is even more striking. One hundred and three cases of type I pneumonia treated with Felton's serum showed a death rate of only 11.7 per cent, while ninety-seven controls had a mortality of 26.8 per cent, two and a half times as high as the treated group.

The favorable results obtained at Bellevue Hospital with Felton's serum, reported by Cecil and Sutliff [16] and in this paper, are fully corroborated by the figures reported for Harlem Hospital in New York by Park, Bullowa and Rosenbluth,[4] who also employed the alternate case method of treatment. One hundred and nine cases of type I pneumonia treated with Felton's serum showed a death rate of 17 per cent, while 105 controls had a mortality of 31 per cent.

TABLE 11.—*Analysis of the Forty-Eight Fatal Cases in the Series Receiving Felton's Concentrated Serum*

Complicating Factors		Number of Cases
Primary	Secondary	
Moribund	Each of these patients recived less than 20 cc. of serum	9
Pneumococcus meningitis.		2
Empyema	1 aged 79 years 1 surgical shock 1 mixed with Streptococcus hemolyticus 1 alcoholism	4
Sepsis with acute arthritis	1 mixed with Friedländer's bacillus..	3
	1 alcoholism and auricular fibrillation 1 aged 59 years and late admission	
Sepsis	5 alcoholism 3 late admission 1 asthma 1 syphilis 1 otitis media	11
Cardiac failure		3
Senility	Ages 62, 65, 76 years	3
Erysipelas	1 pulmonary tuberculosis 1 alcoholism	2
Alcoholism	(2 cases with delirium)	5
Asthma		1
Delirium		2
Late admission		1
None	1 aged 50 years 1 aged 26 years	2
Total		48

Park, Bullowa and Rosenbluth also compared the death rates in treated and untreated septic cases. In twenty-eight septic type I pneumonia patients who received Felton's serum, the death rate was 36 per cent; in twenty-eight control patients with pneumococcus sepsis, the death rate was 71 per cent.

In our experience the administration of concentrated serum has had no appreciable effect on the incidence or death rate of complications.

Analysis of Fatal Cases.—In table 11 are listed the forty-eight patients with type I pneumonia who died in spite of treatment with Felton's serum. Some morbid process other than pneumonia was a factor in nearly every case.

COMMENT

We believe that enough evidence has been submitted in this paper to justify the statement that the various types of pneumonia should be thought of as separate entities. Certainly there is as much difference between type I and type II pneumonia as there is between typhoid and paratyphoid fever. If this is true, the diagnosis is not complete in any case until the type of pneumococcus has been determined. By making use of Sabin's rapid method of typing, the bacteriologic diagnosis can often be determined within a few hours after the clinical diagnosis of pneumonia has been made.

The clinical features of type I pneumonia as stressed in the present study have important diagnostic and prognostic connotations. It is important to appreciate the high incidence of type I pneumonia, its clinical characteristics, and its tendency to frequent complications.

We wish to emphasize once more the variation in the mortality rate for type I pneumonia in different institutions, and for different seasons. It is safe to say that the death rate for type I pneumonia is less than for either type II or type III, but the actual figures vary with the place and the time.

Type I pneumonia is amenable to serum treatment. By the use of serum, a marked reduction in death rate has been reported by many investigators. It is doubtful, however, whether the mortality rate in hospitals will ever be reduced below 10 per cent, as a considerable number of the patients are adults, already afflicted with various systemic and degenerative diseases.

It is difficult to estimate accurately the annual number of type I pneumonias in the United States. However, counting four cases for every death from pneumonia, there are about 480,000 cases of pneumonia in the United States every year. About two thirds of these are of the lobar type and approximately 30 per cent of these, or 96,000 cases, should be type I infections. With a death rate of 25 per cent there would be 24,000 fatalities from type I pneumonia alone. If the figures obtained at Rockefeller, Harlem and Bellevue hospitals are reliable, it seems that from twelve to fifteen thousand lives could be saved annually in the United States by the early and universal administration of type I serum in type I pneumonia.

Type I *unconcentrated* serum has been given a fair trial in private and hospital practice throughout the country but has not been accepted. It has been found unsatisfactory because of its low potency, the frequency of reactions, and the difficulties encountered in its administration.

Felton's concentrated serum has not yet received so extensive a trial; but already its therapeutic value rests on sound experimental and clinical evidence. We cannot agree with Blake [17] or with Cole, who state in recent articles that concentrated serum is still too much in the experimental stage to be advocated for general use. Five years' clinical experience with this product and a marked reduction of the death rate in a large group of cases have convinced us of its therapeutic efficacy.

A comparison of the death rate of patients who received concentrated serum at Bellevue Hospital with that of the patients who received unconcentrated serum at the Hospital of the Rockefeller Insitute is difficult. Cole [11] reports a mortality rate of 10.2 per cent in treated type I patients as compared with 20.1 per cent in our series. It must be borne in mind, however, that the death rate in the untreated group IV cases of his series was only 12.8 per cent, as compared with 31.3 per cent in the Bellevue series; again, in the untreated type II patients, he has reported a death rate of 28.5 per cent as against 48.9 in our series.

17. Blake, F. G.: The Diagnosis and Treatment of Pneumonia, New England J. Med. **202**: 991-995 (May 22) 1930.

With respect to the potency of Felton's serum, we believe that the recent reports of Felton,[15] Goodner [12] and ourselves substantiate the claim that Felton's serum is a concentrated and refined solution of immune bodies approximately ten times as potent as the average unconcentrated serum, the exact ratio depending, of course, on the respective lots of serum used in the comparison. The "unit method" of standardization is an important contribution to the specific therapy of pneumonia, as it affords the physician a fairly accurate gage of the amount of protective substance the patient is receiving.

The incidence of reactions to Felton's serum is much lower than that to unconcentrated preparations. The refined serum in its present form rarely causes thermal reactions. Serum sickness occurred in only 20.6 per cent of a series of 214 patients treated with Felton's serum at Bellevue Hospital. According to Mackenzie and Hanger,[18] 93 per cent of the patients who received unconcentrated serum under their observation developed serum sickness. Furthermore, the serum sickness that occurs after concentrated serum is rarely as severe as that which develops after the use of the unconcentrated preparation.

Finally, the simplified technic used in the administration of the concentrated serum is a great advantage. As doses of from 10 to 20 cc. are adequate, it may be prepared in small vials and readily used when indicated.

SUMMARY AND CONCLUSIONS

1. A series of 3,662 cases of pneumococcus pneumonia in adults and 271 cases in children have been studied clinically and bacteriologically. Of this series 1,161 cases were type I infections and form the basis of this study.

2. Type I pneumonia is considered as a definite clinical entity; it usually runs a typical course, terminates by crisis, and has a high incidence of complications.

3. Type I pneumonia is the most prevalent of all the types, constituting approximately one third of all adult lobar pneumonia treated in Bellevue Hospital. It is quite rare in infants under 3 years of age, but is particularly prevalent in young adults.

4. The mortality rate in 412 patients receiving no serum is 28.2 per cent. For reasons not entirely evident the death rate for type I pneumonia in Bellevue Hospital has shown a steady increase since 1921-1922, when it was 20.0 per cent, to 1928-1929, when it was 42.8 per cent. The death rate for septic type I cases without serum is 66.7 per cent.

5. The evidence in support of the therapeutic value of type I serum is presented from an experimental and clinical standpoint.

6. In a series of 171 cases treated with Huntoon's antibody solution, as compared with an equal number of control cases, the efficacy of the solution is shown by a marked reduction in mortality rate. The disadvantages of this preparation are indicated.

7. Felton's concentrated antipneumococcus serum is described and evidence is presented to show that it is often more than ten times as potent as unconcentrated preparations. A series of 239 cases of type I pneumonia treated with Felton's serum shows a death rate of 20 per cent, as compared with a mortality rate of 31 per cent in a control series of 234 untreated cases. There is a further reduction in death rate to 11.7 per cent in cases treated within seventy-two hours after onset.

8. Type I serum is no longer in the experimental stage. When administered early and in adequate dosage, the clinical results are striking. The present study demonstrates that concentrated serum possesses all the therapeutic value of the unconcentrated preparation. Furthermore, concentrated serum has a much higher potency and a lower content of chill-producing substances and horse serum proteins which make it more easily administered, and less frequently followed by chills, serum reactions and serum sickness.

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18. Mackenzie, G. M., and Hanger, F. M.: Serum Disease and Serum Accidents, J. A. M. A. **94**: 260-265 (Jan. 25) 1930.

STUDIES OF THE ETIOLOGY OF THE COMMON COLD *

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In recent years widespread recognition has come about of the fact that the common cold is not a simple minor infection of the upper respiratory tract which, because of its mild symptomatology, can be conveniently disregarded. The more thorough study of this disease begins to indicate that perhaps it may be the keystone of that complex structure of ills the etiologic agents of which gain entrance to the body by way of the upper respiratory tract. A complete understanding of the pathogenesis of the common cold would not only be of value in solving the nature of this malady itself but would undoubtedly throw important light on the mechanism of all respiratory infection and even perhaps on certain diseases that are not regarded as clearly respiratory in origin.

Information concerning the etiology of the common cold is obviously the sine qua non of the understanding of this infection and of its causal relationship to other disease. Many organisms have at different times been assigned an etiologic rôle and frequently the evidence in favor of one or another agent has been impressive. Many of the organisms described have been comparatively well known and in many instances easy to study bacteriologically. To all students of upper respiratory infections the importance of such organisms has been clear, yet not one of them has maintained its position as the principal initiating agent, but all have sooner or later been assigned a secondary rôle. What, then, is the complex sequence of events in which so many microorganisms seem to participate?

For a number of years we have been studying the problem of the etiology of the common cold. We have sought from the beginning to attain our goal by a process of elimination, realizing, from the beginning, that the final word about the significance of any organism could not be said, at any stage of the investigation, but following the evidence where it seemed to lead in the hope that, in the end, the mechanism of the infection would become clear.

Our first efforts were directed toward displacing the common potential pathogens of the upper respiratory

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* Read before the Section on Pharmacology and Therapeutics at the Eighty-First Annual Session of the American Medical Association, Detroit, June 27, 1930.