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PNEUMOCOCCUS TYPE II PNEUMONIA

A CLINICAL AND BACTERIOLOGIC STUDY OF ONE THOUSAND CASES, WITH ESPECIAL REFERENCE TO SERUM THERAPY *

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In a previous article, we [1] have analyzed 1,161 cases of pneumococcus type I pneumonia treated in the wards of Bellevue Hospital, and have pointed out the beneficial effect of serum therapy in this type of infection. In the present article, we propose to discuss pneumococcus type II pneumonia and to report our results in the treatment of this disease with specific antipneumococcus serum. This investigation comprises 1,000 cases of type II pneumonia from the wards of Bellevue Hospital, and covers a consecutive series except for the year 1925-1926, which is not included because the records for that winter are incomplete. So far as we know, this is the first clinical study ever published in which pneumococcus type II pneumonia is considered as a separate entity. In 1927, Baldwin and Rhoades [2] contributed an article on the specific therapy of type II pneumonia, in which they discussed the effect of type II antipneumococcus serum on twelve cases, but there has been no detailed presentation of this type of pneumonia as a clinical entity.

BACTERIOLOGIC METHODS

From 1920 to 1929, the mouse method of typing sputum described by Avery, Chickering, Cole and Dochez [3] was employed as a routine. The objection to this method lay in the amount of time it involved. On the average, reports were not obtained in less than from eighteen to twenty-four hours, which meant serious delay in the institution of serum treatment. Since 1929, a combination of the original mouse method and the Krumwiede [4] and Sabin [5] methods of typing has been employed, and this procedure has enabled the laboratory worker to report the pneumococcus type on a high percentage of cases within from one to five hours. The actual routine is as follows:

The best specimen of sputum obtainable is sent to the laboratory as soon as the diagnosis of pneumonia has been made. A portion about the size of a bean is emulsified in physiologic solution of sodium chloride and from 0.5 to 1 cc. of this is injected into the peritoneal cavity of a mouse. The remainder of the sputum is typed by the Krumwiede method.[4] If the test gives a positive reading, it is usually accurate. If it is negative or unsatisfactory, the Sabin [5] microscopic method of typing is used by withdrawing a few drops of peritoneal exudate from the mouse and carrying out the agglutination reactions on a glass slide. If neither the Krumwiede nor the Sabin method gives positive reactions, the original mouse method of tube-agglutination and precipitation is performed in full.

If no sputum is available, a generous swab is made from the posterior pharynx and transferred to a tube of broth, which is allowed to incubate for two hours at a temperature of 37 C. One cubic centimeter of this culture is then injected into the peritoneum of a mouse, and microscopic or macroscopic typing is performed as previously outlined. Sputum, of course, is preferable, but the swab method, if properly carried out, gives accurate results. All readings, by whatever method obtained, are confirmed by typing the cultures obtained from the heart's blood of the mouse.

During the past three years, blood cultures were performed on all patients with lobar pneumonia shortly after their admission, and these were repeated daily on patients whose first blood culture was positive, and also on all patients who failed to improve under treatment. The usual procedure was to withdraw 3 cc. of blood from the patient's vein and add 1 cc. to a tube of broth and 1 cc. to each of two pour plates.

Routine cultures were also made from all pleural, pericardial and synovial exudates.

Accuracy of the Combination Method of Typing.—During the season of 1929-1930, specimens of sputum from 196 patients with lobar pneumonia were typed by the rapid methods. Fifty-eight of the 196 cases proved to be pneumococcus type II infections, as checked by cultures from the mouse's heart's blood. Of these fifty-eight cases, twenty-eight provided enough tenacious sputum to be tested by the Krumwiede method, and twenty-five of the twenty-eight gave a sharply positive reaction. In other words, 43 per cent of authenticated type II pneumonias were accurately typed by the Krumwiede method, and in fifty-two of the fifty-eight cases, or 90 per cent of the type II series, positive results were obtained with either the Krumwiede or the Sabin method. Thus, by using one or the other of these rapid methods of typing, 90 per cent of the fifty-eight type II pneumonias were accurately typed in less than five hours, and 43 per cent were successfully typed by the Krumwiede method in less than one hour. The Krumwiede method gave no false readings; the Sabin method only two.

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1. Cecil, R. L.; and Plummer, Norman: Pneumococcus Type I Pneumonia, a Study of Eleven Hundred and Sixty-One Cases, with Especial Reference to Specific Therapy, J. A. M. A. **95**: 1547-1553 (Nov. 22) 1930.
2. Baldwin, H S.; and Rhoades, D. R.: The Specific Therapy of Pneumococcus Type II Pneumonia, Am. J. M. Sc. **174**: 191 (Aug.) 1927.
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. Krumwiede, Charles, Jr., and Noble, W. C.: A Rapid Method for the Production of Precipitin Antigen from Bacteria: An Attempt to Apply It to the Determination of the Type of Pneumococcus in Sputum, J. Immunology **3**: 1-10 (Jan.) 1918.
5. Sabin, A. B.: The Microscopic Agglutination Test in Pneumonia: Its Application to Rapid Typing and Control of Serum Therapy, J. Infect. Dis. **46**: 469-484 (June) 1930.

INCIDENCE

Of the various types of lobar pneumonia, pneumococcus type II ranks second in frequency, being exceeded only by the type I group. Table 1 indicates the relative incidence of the dominant types. In an analysis of 4,310 pneumococcal pneumonias, type I infections were most frequent, comprising 32.1 per cent of the whole series; type II came second with an incidence of 23 per cent, almost a fourth of the series; type III made up only 11.1 per cent. Group IV, which includes a large number of infrequent types, comprised

Table 1.—*Incidence of Pneumococcus Types in Lobar Pneumonia, Bellevue Hospital, 1920-1931* *

Pneumococcus	Number of Cases	Percentage of Incidence
Type I	1,384	32.1
Type II	991	23.0
Type III	477	11.1
Group IV	1,458	33.8
Total	4,310	

* 1925-1926 cases are omitted from this series.

33.8 per cent. These figures, of course, apply to Bellevue Hospital only, but they agree fairly well with those of other institutions. For example, Avery, Chickering, Cole and Dochez [8] report an incidence of 29.3 per cent of type II pneumonia in a series of cases from the Hospital of the Rockefeller Institute, while Park, Bullowa and Rosenblüth [6] found a considerably lower incidence, only 15.6 per cent of type II infections in a series of 793 cases studied at the Harlem Hospital.

Incidence of Type II Pneumonia in Children.—In a series of 329 cases of pneumonia in children at Bellevue Hospital (recently reported by Raia, Plummer and Schultz),[7] only 9 proved to be of type II origin. Three of these occurred in children under 3 years of age, the remaining six in children between 3 and 12 years of age.

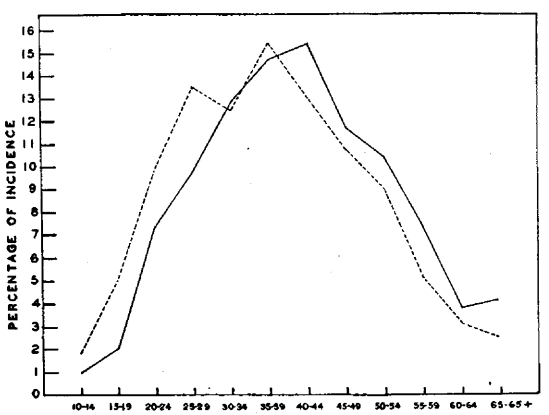

Chart 1.—Age distribution of type I and type II pneumonia, Bellevue Hospital, 1920-1931: solid line, type II pneumonia; broken line, type I pneumonia.

Incidence According to Age.—The age incidence of type II pneumonia corresponds fairly closely with that of type I. In reporting our previous studies,[8] we stated that pneumococcus type I pneumonia was particularly common in young people. This is true also of type II infection, but the difference in age distribution is not as striking as we had anticipated. Thirty per cent of our type I cases occurred in patients under 30 years of age; only 20 per cent of the type II series came within this age limit. This difference is offset by a slightly higher incidence of type II pneumonia in

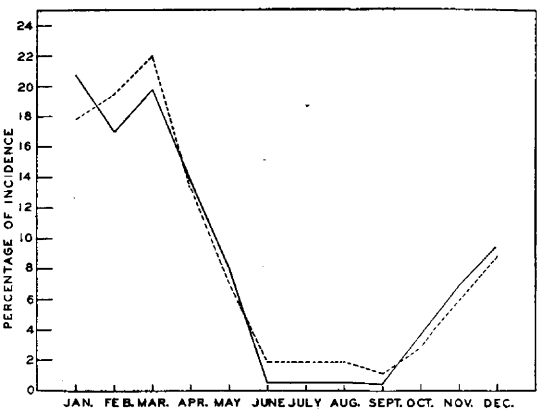

Chart 2.—Seasonal distribution of type I and type II pneumonia, Bellevue Hospital, 1920-1931: solid line, type II pneumonia; broken line, type I pneumonia.

patients between the ages of 30 and 50, and also in those above 50. In table 2 the incidence, according to the various decades, is compared and this is shown graphically in chart 1. From this table the inference can justly be drawn that both type I and type II pneumonia occur chiefly in persons who are still leading active lives and are exposed frequently to contact infections.

In chart 2 the incidence by month of pneumococcus type II pneumonia is compared with that of type I infection. Here, the two types are more closely parallel. For both types the highest incidence is in January, February and March, and the lowest, during the summer months.

Table 2.—*Incidence of Type I and Type II Pneumonia According to Age, Bellevue Hospital, 1920-1931* *

Age	Type I Cases	Incidence, per Cent	Type II Cases	Incidence, per Cent
10–19	94	6.8	30	3.1
20–29	325	23.6	165	16.8
30–39	387	28.0	271	27.6
40–49	298	21.6	266	27.1
50–59	195	14.1	174	17.7
60 and over	81	5.9	76	7.7
Total	1,380		982	

* 1925-1926 cases are omitted from this series.

CLINICAL FEATURES

In our analysis of pneumococcus type I pneumonia, we spoke of type I pneumonia as a typical form of the disease. The same statement applies to the type II infection. Cole,[9] in his De Lamar lecture, states that type I pneumonia and type II pneumonia should be considered specific infectious diseases, just as typhoid is recognized as a specific infection. We are completely in harmony with this point of view. In our experience, it has not been possible to distinguish type I from type II pneumonia clinically, though perhaps it is safe to say that patients with type II infection tend

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

7. Raia, Antoinette; Plummer, Norman; and Shultz, Selma: New Types of Pneumococci in the Pneumonias of Children, Am. J. Dis. Child. **42**: 57-68 (July) 1931.

8. 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.

9. Cole, R. I.: Acute Pulmonary Infections, De Lamar Lectures, 1927-1928, Baltimore, Williams & Wilkins Company, 1928.

to be more toxic and that their sputum is more prone to be markedly rusty and tenacious.

COMPLICATIONS

The incidence of complications in type II pneumonia varies but slightly from that in type I, except in respect to empyema, which occurs about half as frequently in the former as in the latter group. This is shown not only in the table of clinical complications (table 3) but also in the table of complications listed from autopsy observations (table 4). In Locke's study of 478 cases of empyema,[10] the preponderance of pneumococcus type I complications in the pleura is much more marked than in our own series. He found that in forty-nine cases of empyema 48.4 per cent yielded pneumococcus type I, while only 5.2 per cent were of type II origin.

It is interesting to note, as shown in table 4, that pneumococcus endocarditis occurred twice as frequently in type II as in type I pneumonia. This is probably related to the high incidence of pneumococcus bacteremia in type II pneumonia, a feature that will now be discussed.

BACTEREMIA

In a total of 202 cases in which no serum was administered, 162, or 46.4 per cent, showed type II pneumococci in the blood, yielded by culture at some time

TABLE 3.—*Complications in Type I and Type II Pneumonia of Adult Patients*

Complications	Type I (1,131 Cases)	Percentage of Incidence	Type II (991 Cases)	Percentage of Incidence
Empyema	73	6.5	38	3.8
Meningitis	20	1.8	24	2.4
Acute arthritis	10	0.9	5	0.5
Suppurative pericarditis	7	0.6	3	0.3
Endocarditis	4	0.4	12	1.2
Phlebitis	5	0.5	8	0.8
Pleurisy with effusion	26		15	
Cellulitis	32		17	
Cardiac irregularity	26		24	
Pneumothorax	3		..	
Lung abscess	4		5	
Parotitis	5		2	

or other during the course of the disease. This is considerably higher than the figure which we obtained for type I pneumonia (29.7 per cent) and goes far to explain why type II pneumonia is such a serious infection.

MORTALITY RATE

Table 5 shows the annual mortality rate for type II pneumonia from 1920 to 1931. None of the patients listed in this table received serum. The annual rate varies from 38.7 to 57.2 per cent. Some of this variation, perhaps most of it, is due to the fact that the number of cases for each year is comparatively small. The total of 441 cases showed a death rate of 48.8 per cent. In other words, practically half of the type II pneumonias at Bellevue Hospital end fatally. While the result is consistent with the type of patient treated in this hospital, it is interesting to compare this death rate with that of 28.5 per cent reported by Cole[9] from the Hospital of the Rockefeller Institute, and with that of 30 per cent reported by Park, Bullowa and Rosenblüth[6] in the Harlem Hospital. Undoubtedly, the general physical condition of the patient has a great deal to do with the outcome in this as in other types of pneumonia. We have reason to believe that the high incidence of alcoholism is a factor in the high death rate at Bellevue.

10. Locke, E. A.: Acute Empyema, New England J. Med. **203**: 391-398 (Aug. 28) 1930.

Our figures show a definite relationship of bacteremia to the mortality rate in type II pneumonia. In the series that received no serum, sixty-four cases with bacteremia showed a death rate of 87.5 per cent, while seventy-one cases with sterile blood cultures yielded a death rate of only 8.5 per cent. The close relation between bacteremia and the mortality rate has been

TABLE 4.—*Complications in Type I and Type II Cases—Autopsies*

Complications	Type I (52 Cases)	Percentage of Incidence	Type II (79 Cases)	Percentage of Incidence
Empyema	14	26.9	9	11.4
Meningitis	6	11.5	10	12.7
Endocarditis	3	5.8	9	11.4
Suppurative pericarditis	2	3.8	2	2.5
Lung abscess	1	1.9	3	3.8
Miliary lung abscess	2	3.8	3	3.8

stressed in our previous studies and by other observers, but it is particularly well illustrated in pneumococcus type II infections.

The death rate for type II pneumonia at Bellevue Hospital is almost twice as high as that for type I, 48.8 per cent versus 28.2 per cent. It is interesting to note how closely these figures compare with the incidence of bacteremia in these two types of pneumonia:

Type	Bacteremia Per Cent	Death Rate Per Cent
Pneumococcus type I pneumonia	29.7	28.2
Pneumococcus type II pneumonia	51.1	48.8

The mortality is not only closely related to the presence or absence of bacteremia but is also dependent in great measure on the number of organisms present in the blood stream. Three patients who received no serum showed 22, 25 and 68 colonies of type II pneumococcus in their blood culture plates but, in spite of this handicap, recovered. Except for these three cases, no patient recovered who had more than 5 type II pneumococci per cubic centimeter of blood. This statement, of course, applies only to patients who received no serum. The serum-treated patients will be discussed later.

There also appears to be some difference in the significance of early and late bacteremia. An early bacteremia, if not severe, is sometimes overcome; that developing late in the disease is practically always fatal.

TABLE 5.—*Annual Mortality Rate of Patients with Type II Pneumonia Not Receiving Serum, Bellevue Hospital*

Year	Number of Cases	Deaths	Mortality Rate
1920–1921	32	13	40.6
1921–1922	42	17	40.5
1924–1925	30	15	50.0
1926–1927	31	15	48.4
1927–1928	77	44	57.2
1928–1929	69	34	49.3
1929–1930	62	24	38.7
1930–1931	98	53	54.1
Total	441	215	48.8

The mortality rate for type II pneumonia varies, of course, with the age. Between the ages of 20 and 30 the death rate in the present series was only 22.2 per cent, while in patients over 60 the death rate was 78.5 per cent. The mortality rate was also closely related to the complications. All the patients who developed pneumococcus meningitis, endocarditis or peritonitis died. Thirty-eight patients with empyema showed a death rate of 50 per cent.

SPECIFIC TREATMENT

In our recently published study of pneumococcus type I pneumonia, we reported a series of 239 cases of type I infection treated with concentrated and refined antipneumococcus serum, compared with a control series of 234 untreated cases. The death rate in the latter was 31 per cent, as compared with only 20 per cent in the serum-treated cases, and there was a still further reduction to 11.2 per cent in cases treated within seventy-two hours after onset. From experimental, clinical and statistical evidence, we concluded that type I antipneumococcus serum, when administered early and in adequate doses, usually yielded satisfactory results.

During our study of the specific treatment of type I pneumonia, we became interested in the subject of serum therapy for type II pneumonia. Since the death rate in type II infections is approximately twice that in type I, the need of some form of specific treatment is obvious. Furthermore, there is such a close bacteriologic relationship between pneumococcus type I and pneumococcus type II, and so much clinical resemblance in the infections which they produce, that a certain similarity in their response to specific serum would seem reasonable. However, certain fundamental differences between the two diseases do exist. In the first place, the very fact that type II pneumonia is such a fatal infection means that, in order to be efficacious, a serum must be administered early in the course of the disease and must be of high potency. Secondly, according to the work of Dochez and Avery,[11] there is a greater amount of soluble substance in the blood and urine of a patient with type II pneumonia than in that of a patient with a type I infection. The serum, to be efficient, must neutralize all this soluble substance and must eliminate from the blood stream the pneumococci which are usually present in severe cases. This again calls for the administration of a highly potent serum early in the disease. Attempts to meet these requirements encounter great difficulties because, although it is important to have a highly potent serum for the treatment of type II pneumonia, the serum produced by immunizing horses against pneumococcus type II is usually much lower in content of agglutinins, precipitins, and other protective bodies than a good type I serum.

In a previous article, we pointed out the experimental, clinical and statistical evidence that has been accumulated in favor of type I serum, but so far the evidence in support of type II serum is largely of a theoretical or experimental nature. Various laboratory animals can be immunized with killed cultures against pneumococcus type II infection, and mice can be uniformly saved from a fatal type II sepsis if sufficient type II serum is injected simultaneously with the culture. Cecil and Steffen[12] found that Huntoon's pneumococcus type II antibody solution possessed the faculty of sterilizing the blood in type II pneumonia in monkeys, provided the sepsis was not too severe at the time the serum was introduced. So far as clinical evidence in favor of an efficacious type II serum is concerned, there is some difference of opinion. Cole,[13] for example, treated a small series of type II pneumonias with homologous antipneumococcus serum and was quite discouraged with the results obtained. In 1917 Avery, Chickering, Cole and Dochez[3] said: "The serum of type II is much less efficacious. Indeed, it has not yet been thoroughly demonstrated whether it has any practical effect on the outcome of the disease or not." Cole's explanation of the inefficacy of type II serum was that it was not sufficiently potent. He says: "Whereas the horse serum against type I infection is of such a strength that 0.2 cc. will regularly protect a mouse against 0.1 cc. of virulent culture, it has been impossible to produce an immune type II serum of any greater activity than that 0.2 cc. will protect a mouse against 0.01 cc. of culture."

Ten years later, however, we were able to obtain from the New York City Board of Health a type II antipneumococcus serum of such potency that 0.2 cc. would protect a mouse against 0.2 cc. of virulent type II culture. In other words, the serum was twenty times as potent as that employed by Cole and his co-workers in their therapeutic experiments with type II serum. The results obtained with this serum were more encouraging than those reported by Cole and were made known in an article by Baldwin and Rhoades[2] in 1927. These writers succeeded in sterilizing the blood of a small number of patients with type II pneumonia, and, furthermore, they noted some rather striking clinical reactions in certain type II cases which they had treated early in the course of the disease.

These earlier investigations with type II antipneumococcus serum demonstrated quite clearly that if the serum were to be of any value at all it would have to be employed in a highly concentrated form. Gay and Chickering,[14] in 1915, found that by mixing immune serum with a solution of pneumococcus bodies of the same type, a precipitate was formed which contained most of the protective substance of the serum. This could be dissolved in an akaline medium and a clear solution of pneumococcus antibodies obtained. In 1921, Huntoon[15] modified this method, using the washed pneumococcus bodies, and thus produced a therapeutic agent practically free from serum protein, and fairly potent in protective substance against type I and type II pneumococcus. Felton,[16] in 1924, found that practically all the protective substance could be obtained in a precipitate formed by adding the serum to a large amount of distilled water. More recently, Felton[17] has combined the salting-out method of Avery with his own, to refine and concentrate to a further degree the pneumococcus serum for therapeutic use.

INVESTIGATION AT BELLEVUE HOSPITAL

Our first experience with the specific treatment of type II pneumonia was in 1920, when we undertook to investigate the immunologic and therapeutic properties of Huntoon's "pneumococcus antibody solution." This product was not a serum but an aqueous solution of immune bodies which had been removed from antipneumococcus serum by adding to it an excess of pneumococci and later dissociating the immune sub-

11. Dochez, A. R.; and Avery, O. T.: The Elaboration of Specific Soluble Substance by Pneumococcus During Growth, J. Exper. Med. **26:** 477 (Oct.) 1917.

12. Cecil, R. L., and Steffen, G. I.: Studies on Pneumococcus Immunity: V. The Treatment of Experimental Pneumococcus Pneumonia in Monkeys with Pneumococcus Antibody Solution, Bull. 141, Hyg. Lab., April, 1925.

13. Cole, Rufus: The Neutralization of Antipneumococcus Immune Bodies by Infected Exudates and Sera, J. Exper. Med. **26:** 453 (Oct.) 1917.

14. Gay, F. P.; and Chickering, H. T.: Concentration of the Protective Bodies in Antipneumococcus Serum by Means of Specific Precipitation, J. Exper. Med. **21:** 389-400, 1915.

15. Huntoon, F. M.: Antibody Studies: I. Reversal of the Antigen-Antibody Reaction; II. The Recovery of Antibody from Sensitized Antigens: Technic; III. Chemical Nature of Antibody, J. Immunology **6:** 117-200 (March) 1921.

16. Felton, L. D.: A Study of the Isolation and Concentration of the Specific Antibodies of Antipneumococcus Sera, Boston M. & S. J. **190:** 819-825 (May 15) 1924.

17. Felton, L. D.: Concentration of Pneumococcus Antibody, J. Infect. Dis. **43:** 543-553 (Dec.) 1928.

stances from the bacteria. Huntoon's antibody solution was polyvalent, but its protective power against type II was not as high as against type I. The results of our two years' experience with Huntoon's antibody solution [18] have been published in full. Eighty-three cases of type II pneumonia, admitted to six medical wards of Bellevue Hospital, were treated with antibody solution and showed a death rate of 27.7 per cent. Sixty-seven control cases, admitted to six other medical wards during the same period of time, received no specific treatment and showed a death rate of 40.3 per cent. These figures were slightly in favor of the treated group, but the series was too small to have much significance. Because of its low potency and its tendency to produce severe chills, we abandoned the use of Huntoon's antibody solution in 1922. This experiment, however, showed the desirability of obtaining some form of purified serum. Huntoon's antibody solution was practically free from horse protein, so that its administration was never followed by anaphylactic reactions or serum sickness.

FELTON'S CONCENTRATED SERUM

From 1924 to the present time, Felton's concentrated antipneumococcus serum has been used at Bellevue Hospital. The method of preparation of this serum has been described in previous articles by us and in Felton's own papers.[19] The finished product is a slightly opalescent aqueous solution, rich in pneumococcus immune bodies.

TABLE 6.—*Comparison of the Common Immunologic Reactions of Type II Pneumococcus Serum and Its Concentrate (Felton)*

	Serum	Concentrate
Precipitins	25–100*	200–2,000
Agglutinins	20	300
Complement fixation	20	120
Opsonins	40	320
Bactericidal action†	5×10^2	2×10^5
Protection	400	3,000
Neutralization	25	300

* The figures indicate the highest dilutions giving positive reactions.
† The figures indicate the actual number of bacteria killed.

The potency of Felton's serum varies with different lots, but manufacturers overcome this difficulty by pooling the serum from several horses. The actual ratio of the potency of the concentrated to that of the unconcentrated serum has been difficult to determine, for the reason that laboratories have employed different methods of standardization. Felton,[20] however, has recently published an article in which he presents a comparison of the common immunologic reactions of unconcentrated serum with those of the concentrated product. This is shown in table 6. The concentrated type II serum was prepared from a certain lot of standard serum and then compared with the original serum in respect to its content of immune bodies. It was found to contain far more precipitins, agglutinins, opsonins and other protective substances than the original serum. The difference in protection is particularly marked and in this experiment indicates that the concentrate was about eight times as potent as the unconcentrated serum.

From 1924 to 1930 we conducted a carefully controlled therapeutic experiment with Felton's serum on patients with type II pneumonia. The alternate case method was used in our investigation; that is, every patient diagnosed as having lobar pneumonia was given a number, and those with even numbers received serum, while those with odd numbers served as controls. The method of administering the concentrated serum has been described in detail in a previous article. After a preliminary test for sensitiveness to horse serum, 5 cc. of concentrated serum was slowly injected intravenously. If no reaction occurred, from 10 to 20 cc. was introduced into the blood stream one or two hours later, the dose depending on the potency of the preparation and the severity of the case. In general, we tried to administer from 100,000 to 200,000 units (from 40 to 100 cc.) during each twenty-four hour period until the patient showed definite signs of recovery or until it was evident that the serum was exerting no influence whatever on the disease.

The effect of type II serum on the clinical course of the disease is not by any means as striking as that produced by serum in type I pneumonia. Even when patients are treated very early, a rapid drop in temperature with concomitant improvement is rarely achieved. There is, however, a definite impression among most of the clinicians who have followed type II serotherapy that the symptoms of toxemia are usually less pronounced in the treated cases.

EFFECT ON BACTEREMIA

One of the most important problems in this study was to determine the effect of type II serum on pneumococcus type II bacteremia. As has already been stated, the outcome of a case of type II pneumonia depends to a great extent on whether or not the blood remains sterile. The figures cited in the untreated cases showed a mortality rate of only 8.5 per cent when the blood cultures remained negative, as against 87.5 per cent when the patients became septic. Furthermore, only two of the patients in our entire control series whose blood contained more than 10 type II organisms per cubic centimeter recovered. With these facts in mind it seemed reasonable to assume that, if concentrated serum was potent enough to sterilize the blood, it would have a favorable effect on the outcome of the disease.

Under certain circumstances, Felton's type II serum has, without doubt, the capacity to sterilize the blood and to keep it sterile. In most of the early cases with beginning septicemia the blood culture became negative when sufficient serum was administered, and as a result the chances of recovery seemed to be greatly increased. Charts 3 and 4 show the clinical courses of two such cases. In both patients, a definite therapeutic effect was apparently achieved by the prompt administration of serum. At any rate, they show a course not taken by our control cases. Large amounts of serum will practically always sterilize the blood of even late type II cases with marked sepsis, but this accomplishment usually has no effect on the final outcome of the disease. A remarkable case in our series had innumerable colonies of type II pneumococcus in the blood on admission, as shown in a 1 cc. pour-plate culture. The blood was successfully sterilized with large amounts of serum, but empyema developed, followed by a lung abscess, and the patient died eight months later.

Chart 5 clearly shows that sepsis was more marked in the treated patients who recovered than in the

18. 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.
19. Felton (footnotes 16 and 17).
20. Felton, L. D.: The Concentration of Antipneumococcus Serum, J. A. M. A. **94**: 1893-1896 (June 14) 1930.

controls. *Twenty-three septic patients who received serum recovered while only ten without serum got well.* The maximum number of organisms in 1 cc. of blood was 333 in the treated series; 68 in the control. Furthermore, nine of the serum treated group had more than 10 pneumococci in each cubic centimeter of blood; only two of the control group had such a quantity.

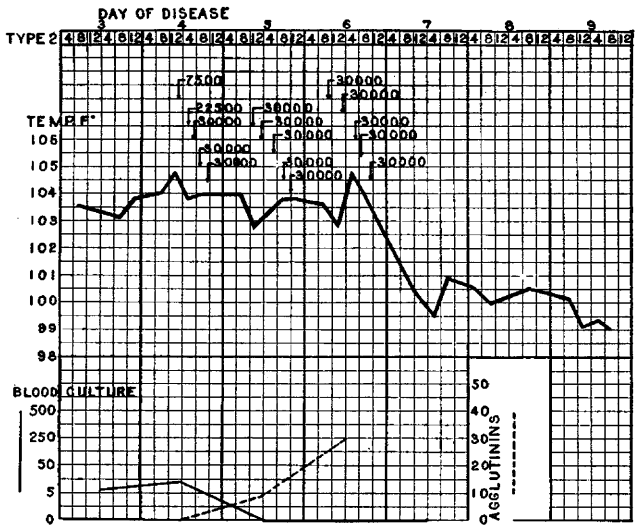

Chart 3.—Temperature, results of blood culture, and agglutinin titer of F. H., aged 26, with type II pneumococcus pneumonia, admitted to Bellevue Hospital on the third day of his illness. The blood culture on the day of admission showed 8 type II pneumococci per cubic centimeter of blood, and on the next day, the fourth day of the patient's illness, 22 organisms. On that day, 80 cc. (120,000 units) of Felton's concentrated serum was given intravenously, and the following day the blood was sterile with a moderate amount of type II agglutinins. On the fifth and sixth days, serum therapy was continued (100 cc., 150,000 units each day). The blood remained sterile, the agglutinins rose rapidly, and the patient had a temperature crisis on the seventh day.

Since 1928, blood cultures have been taken as a routine on all patients included in the type II series. In the septic cases the mortality rate for the control group has been 88 per cent; for the treated group, 69 per cent. The capacity on the part of type II serum to prevent bacteremia is further shown by the fact that,

TABLE 7.—*Comparison of Mortality Rate 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	30	10	33.3	29	14	48.3
1926-1927	29	12	41.4	31	15	48.4
1927-1928	73	28	38.4	71	38	53.5
1928-1929	64	30	46.8	64	29	45.3
1929-1930	56	22	39.3	58	20	34.5
Total	252	102	40.5	253	116	45.8

* Patients dying within twenty-four hours are not included.

while 91 per cent of the untreated patients who died had positive blood cultures, 74 per cent of the treated died with bacteremia.

EFFECT OF TYPE II SERUM ON MORTALITY RATE

The effect of concentrated type II serum on the mortality rate of type II pneumonia is indicated by the year in table 7. Altogether 252 cases of type II pneumonia have been treated with concentrated type II serum, with a death rate of 40.5 per cent, while 253 alternate controls show a mortality of 45.8 per cent. The difference in the rates of the two groups is certainly not striking. Furthermore, it will be noticed that for two seasons the death rate in the treated series was slightly higher than that in the control.

It is interesting to compare the results of serum treatment in type II pneumonia at Bellevue Hospital with the results of well controlled series in other institutions. In table 8 the results of previously published studies are summarized. This comparison suggests more promising results for type II serum than were indicated in our own experience. All these investigators used Felton's serum and each used the alternate

TABLE 8.—*Comparison of Mortality Rate in Cases Treated with Felton's Concentrated Serum and Control Cases*

Investigators	Treated Cases	Treated Deaths	Treated Mortality, per Cent	Control Cases	Control Deaths	Control Mortality, per Cent
Finland: New England J. Med. **202**: 1244 (June 26) 1930	39	11	28.2	32	11	34.4
Park, Bullowa and Rosenblüth [6]	56	13	23.0	61	18	30.0
Baldwin: Am. J. M. Sc. **181**: 788 (June) 1931	35	9	25.7	29	15	51.7
Cecil and Sutliff: J. A. M. A. **91**: 2035 (Dec. 29) 1928*	102	40	39.2	102	53	52.0
Total	232	73	31.4	224	97	43.3

* This series is included in the present study.

case method of control. In the total series the mortality rate in 232 cases of type II pneumonia treated with Felton's serum is 31.4 per cent, while in the 224 control cases it is 43.3 per cent.

Although our own figures gave little, if any, evidence in support of type II concentrated serum, the more favorable results obtained by other investigators, as well as our own encouraging experience in early septic cases, led us in the fall of 1930 to continue the investigation. At that time, however, it was decided to limit serum treatment to patients admitted to the hospital within seventy-two hours of the onset of their

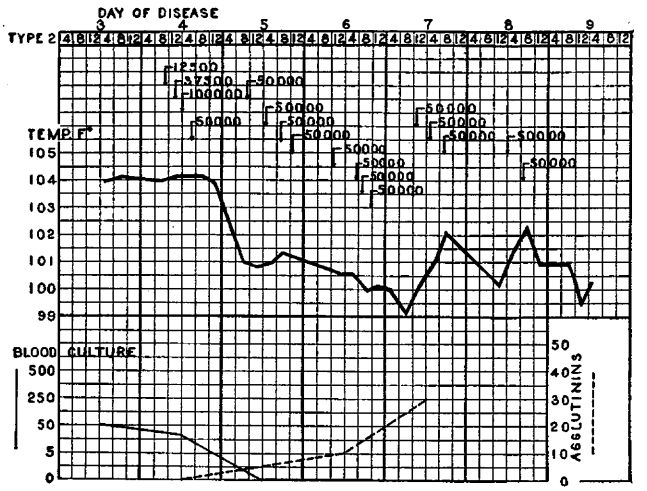

Chart 4.—Temperature, results of blood culture, and agglutinin titer of J. C., aged 44, with type II pneumococcus pneumonia, admitted to Bellevue Hospital on the third day of his illness. The blood culture on the day of admission showed 59 type II pneumococci per cubic centimeter of blood, and on the following day, the fourth day of the patient's illness, 28 organisms. On that day, 80 cc. (200,000 units) of Felton's concentrated serum was given intravenously. The temperature dropped from 104 to 101 F., the blood became sterile, the agglutinins in the blood began to rise, and the patient appeared less toxic. Serum treatment was continued on the fifth, sixth, seventh and eighth days of the illness to insure protection against a relapse.

infection, as it was thought that if the serum had any value it would be most evident in the early cases; moreover, it would be possible to give thorough serum treatment and more careful study to the smaller series.

The results of our 1930-1931 study, shown in table 9, are rather surprising. There were twenty control cases with thirteen deaths (65 per cent); and twenty-one cases treated with serum, with three deaths (14.3 per cent). Table 10 shows that the age and other complicating factors were slightly against the control cases, but not to such a degree as to be responsible for the marked difference in mortality rate. Furthermore, of all the patients who recovered, only two controls were septic, while six who were treated had pneumococci in the blood stream. These results are very encouraging but cannot be considered conclusive, because of the small number of cases in the series.

TABLE 9.—*Comparison of Mortality Rate in Cases Treated with Felton's Concentrated Serum and Control Cases Admitted Within Seventy-Two Hours of Onset 1930-1931*

	Number of Cases	Deaths	Mortality, per Cent
Control	20	13	65.0
Treated	21	3	14.3

COMMENT

The present investigation has served to demonstrate that type II pneumonia, as it occurs in Bellevue Hospital, is one of the most serious infections encountered in this climate. The incidence of type II is considerably less than that of type I pneumonia, but the mortality rate is so much higher that the actual number of deaths resulting from type II pneumonia is greater than that from type I. The two diseases run a somewhat similar clinical course. However, empyema is a more frequent complication in type I pneumonia, while bacteremia is much more common in type II infection. Bacteremia is probably an important factor in the high death rate in type II pneumonia.

The time has come when we must think of the various pneumococcus "types" as etiologic agents of independent diseases. Such an attitude is necessary before the specific treatment of pneumonia can be put on a rational basis; and, furthermore, this etiologic diagnosis is of definite aid to the physician in making a prognosis. Let us visualize two patients with pneumonia on the fifth day of the disease, each with two lobes involved, and with a temperature of 104 F. What a difference there is in prognosis, if one patient has a type I infection with a sterile blood culture, and the other, a type II, with bacteremia! The former patient will probably recover; the latter will almost certainly die.

TABLE 10.—*Analyses of 1930-1931 Series*

	Control	Treated
Average age	42 years	37 years
Number over 50 years	4	3
Bacteremia on admission	9	7
Complicating systemic disease	5	6
Chronic alcoholism	8	7

The rapid methods of typing described in this article are comparatively simple and make it possible for the physician to know the pneumococcus type on the same day that the diagnosis of pneumonia is made. About 55 or 60 per cent of cases will fall into either the type I or the type II group. Every patient with type I pneumonia should have serum treatment. In this article we have presented evidence that concentrated and refined serum has some therapeutic value in the treatment of type II pneumonia. Certainly, it appears more promising than any other form of specific treatment available. The carbohydrate-splitting enzyme that Avery and Dubos [21] have isolated offers hope for the eventual control of type III pneumonia, but thus far no enzyme has been discovered which affects type II organisms. Pneumococcus vaccine is being advocated by some for the treatment of all types of pneumonia, but evidence has not been furnished to prove that it affects the course or mortality rate of lobar pneumonia. Reports [22] have appeared recently which show a marked reduction in mortality rate following the use of vaccine, but the cases were not sufficiently studied, either clinically or bacteriologically, nor was the series well enough controlled to make the conclusions justifiable.

In attempting to evaluate the statistical evidence in support of type II serum, it must be remembered that the product which was used in the first years of our investigation was not nearly as potent as that which is now available. During the season of 1930-1931, the death rate in a group of twenty-one serum treated cases (admitted to the hospital early) was only 14.3 per cent, compared with 65 per cent for twenty early controls. This series of cases is too small to carry much significance. If, however, such a marked difference in mortality rate is maintained through the next two or three seasons, it will serve as strong evidence in favor of serum treatment.

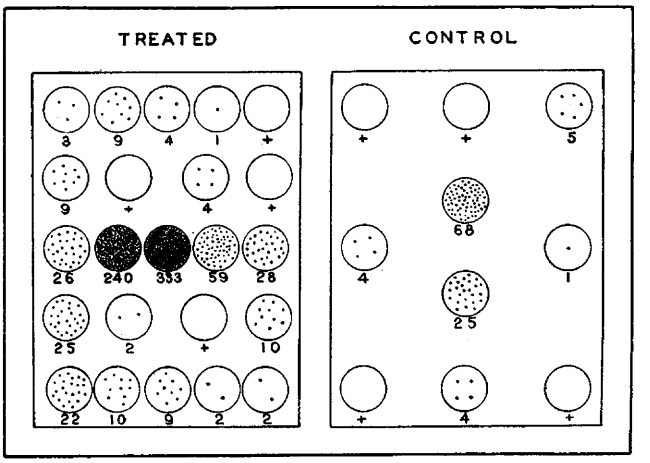

Chart 5.—Figures showing the results of blood culture in patients who recovered from type II pneumococcus bacteremia. One panel refers to the treated, and the other, to the control cases. The circles represent blood culture plates, and the dots, colonies of pneumococci. The circles without dots and with a plus (+) sign denote cultures in which the broth only was positive.

The effect of type II serum on the clinical course of type II pneumonia is certainly not as striking as that produced by refined serum in type I pneumonia. The sharp drop in temperature so often achieved in cases of type I infection treated early with serum is rarely obtained in type II cases. Serum-treated patients, however, appear less toxic and seem to run a somewhat milder course than the untreated.

Additional evidence in favor of type II serum lies in its effect on type II bacteremia. This is shown in a reduction of the mortality rate from 88 per cent in the septic cases without serum to 69 per cent in the septic cases with serum. An analysis of the recovered

21. Avery, O. T., and Dubos, René: The Protective Action of a Specific Enzyme Against Type III Pneumococcus Infection in Mice, J. Exper. Med. **54**: 73-89 (July) 1931.
22. Sutton, D. C.; Kendall, A. I., and Rosenblum, Albert: Immunizing Value of "Natural Bacterial Antigens," Study No. 1—Pneumococci, Am. J. M. Sc. **182**: 454-459 (Oct.) 1931.

cases also shows a striking difference in the degree of bacteremia in the treated and untreated groups. This is clearly demonstrated in chart 5.

It is too early to pass final judgment on the efficacy of type II serum. More investigation with a highly potent product is required before a fair verdict can be given. It is significant, nevertheless, that those who have worked extensively with type II serum are confident that it has a place in the treatment of type II pneumonia.

SUMMARY AND CONCLUSIONS

1. This report is based on a clinical and bacteriologic study of 1,000 cases of pneumococcus type II pneumonia from the wards of Bellevue Hospital.

2. The bacteriologic and clinical methods employed are described. During the last three years of the study, particular attention has been given to rapid methods of typing the sputum.

3. Pneumococcus type II pneumonia is considered from the standpoint of a specific disease entity. Like type I pneumonia, it runs a characteristic febrile course, usually terminating by crisis.

4. Twenty-three per cent of 4,310 cases of pneumococcus lobar pneumonia in adults were type II infections. Only 9 out of 329 cases of pneumonia in children were of type II origin.

5. Curves of the age distribution of type I and type II pneumonia show a higher incidence of type I up to the age of 30, and a slightly higher incidence of type II beyond that age. Curves of the seasonal distribution of the two types are almost identical.

6. The incidence of complications in the entire series as well as in the cases that came to autopsy is tabulated for both type I and type II pneumonia. Empyema occurs twice as frequently in type I, while endocarditis is found twice as often in type II. Meningitis has the same incidence in both types. Bacteremia is almost twice as prevalent in type II as in type I infections.

7. Type II pneumonia has a mortality rate of 48.8 per cent, almost twice that of the type I variety. The death rate in septic type II cases is extremely high, 87.5 per cent in the present series.

8. The experimental evidence in support of type II serum and its concentrate is presented. The immune serum contains antibodies which react against the type II organism, and it also regularly protects mice and other laboratory animals from type II infection. Felton's concentrated serum is shown to be from six to twenty times as high as unrefined serum in its content of antibodies and protective substance.

9. A definite clinical effect following the early administration of concentrated type II serum is often demonstrable. The course of the disease is usually milder and the blood more frequently remains sterile.

10. In a series of 252 cases of type II pneumonia treated with Felton's concentrated serum the mortality rate was 40.5 per cent as compared with a death rate of 45.8 per cent in 253 alternate controls. During the last year of our investigation, only early cases of type II pneumonia were included in the therapeutic study. Twenty-one treated cases had the benefit of intensive serotherapy with a death rate of only 14.3 per cent, against a rate of 65 per cent for twenty controls. The latter series, however, is too small to be convincing.

11. The results presented in this paper indicate that type II concentrated serum has definite though not striking clinical value. At the present time it is the most promising therapeutic agent available for the treatment of this disease.

THE MANAGEMENT OF BREAST CANCER *

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LOS ANGELES

There are two distinct surgical methods for carcinoma of the breast, one radical, the other conservative. The conservative operator advocates a simple removal of the offending neoplasm without any attempt to extirpate glands from the surrounding areas, while the radical performer encourages the obliteration of all questionable tissue, including muscles and fascia, and the cleaning out of all gland-bearing spaces contiguous to the cancer field.

Among radiation therapeutists there is a similar dual point of view. Many radiologists are inclined to the use of light exposures in order to obtain palliation without endangering normal structures around the field; others take the opposite point of view and maintain the necessity of destroying all cancer cells in the involved area as well as every aberrant cell contiguous to the affected field. As with surgery so also with radiology; the two groups can find ample grounds on which to found their separate claims.

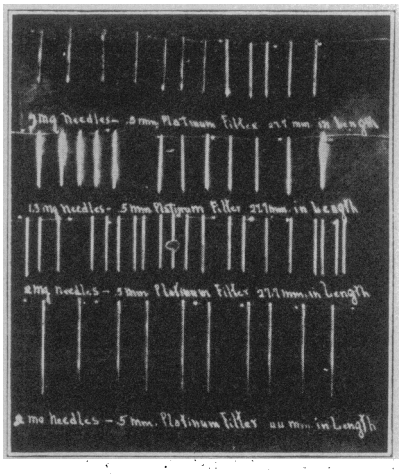

Fig. 1.—Types of radium filled platinum needles.

It was my privilege to present, at the London Congress in 1925, a paper on "The Treatment of Cancer of the Breast from the Viewpoint of a Radiologist," containing statistics of our own clinic, covering 550 patients observed over a sufficient length of time to warrant a report. In the intervening six years, many changes have occurred as related both to basic knowledge and to treatment methods. I have now modified and revised, to a considerable degree, my opinion of radium needles as then expressed.

My first success with radiation in a recurrent breast cancer was reported in 1901. Since then, upward of 3,000 patients with cancer of the breast have received treatment at our clinic. Obviously, it was impossible in earlier days to compile an accurate statistical study; therefore, only 550 patients were referred to in 1925.

Since then our recording and follow up methods have been greatly improved but, even yet, to obtain accurate and reliable cancer statistics is well nigh impossible. The ratio obtained in our 1925 report has not been materially increased in advanced cases; however, with the constantly increasing public knowledge regarding cancer, a greater number of patients are submitting to treatment at a sufficiently early stage to presage a definitely higher total of five-year clinical cures. Familiarity with the evolution of radiation standards will, no doubt, permit one to coincide with this conclusion.

* From the Soiland Clinic.
* Read before the Cancer Symposium at the Third International Congress of Radiology. Paris, July 30, 1931.