EFFECTS OF EARLY SERUM TREATMENT ON PNEUMOCOCCUS TYPE I PNEUMONIA.

By RUSSELL L. CECIL, M.D.,
NEW YORK CITY.

It is a fundamental principle in all serum therapy that to obtain the best results the serum must be given early in the disease. This statement holds true regardless of whether one is using antitoxic or antibacterial serum. During the past decade, there have appeared in American and British medical literature a goodly number of reports on the successful use of refined and concentrated antipneumococcus serum in the treatment of pneumococcal pneumonia. The majority of these reports have dealt with pneumococcus Type I infections. More recently, however, a number of articles have appeared, reporting favorable results with serum in the treatment of other types of pneumococcal pneumonia. Promising figures have been submitted for the serum treatment of Types II, V, VII, VIII and XIV. The most significant feature of these reports on serotherapy is that they are all, without exception, favorable. I cannot recall a single skeptical article since the introduction of Felton's concentrated serum. Many of the authors, after reporting their results on a series of cases studied, have given mortality figures for cases treated during the first three or four days of the disease. In every case, the mortality rates for cases treated early are distinctly lower than the death rate for the whole series, and much lower than the death rate for cases treated late in the disease.

It occurred to the writer that an analysis of a series of cases of pneumococcus Type I pneumonia, in which serum was administered unusually early in the course of the disease, that is, during the first twenty-four hours of the infection, might throw some interesting light on the ultimate possibilities of serum therapy in this type of pneumonia. Not so very long ago I made the statement that it was doubtful whether the death rate for Type I pneumonia could be reduced below ten per cent by means of serum therapy. This statement was based on the observation that so many patients with pneumonia

suffer from some previous depleting condition, such as influenza, child-birth, surgical operations, or some chronic systemic diseases, such as tuberculosis, diabetes, cancer, etc. By way of contrast I had in mind diseases like diphtheria and scarlet fever which occur almost exclusively in healthy children and where the physician has only one medical problem, namely, the acute infection to combat. However, figures which I shall presently show, indicate that I may have been too pessimistic in my prognostications.

Let us now consider briefly the various phenomena which are manifest when concentrated antipneumococcus Type I serum is administered quite early in Type I pneumonia. A very frequent and happy manifestation of early serum treatment of Type I pneumonia is a complete and dramatic abortion of the infection. The patient, from having been acutely ill, with a high temperature, pleuritic pain, marked restlessness, and paroxysms of coughing, suddenly finds himself well. The temperature is normal or subnormal. The pulse and respiration return to their usual rates. Pleuritic pain disappears and the cough is ameliorated. From being a serious, exhausting, seven or eight-day infection, the disease is reduced to the status of a brief influenzal attack. We believe that these instances of dramatic termination are explained by the fact that in the early phases of the disease, before frank consolidation has developed to its maximum intensity, the specific antibodies of the serum are capable of so affecting the pneumococci in the pulmonary lesion as to bring about a rapid cessation of the infection. Once consolidation is complete, the circulation through the affected lobe is seriously interfered with. After this stage has been reached, usually by the third or fourth day of the disease, the chief effect of the injected immune bodies is to confine the pneumococci to the pulmonary lesion, and to prevent extension of the pathological process. Under the latter circumstances the actual termination of the disease is brought about by the process of natural recovery. This point of view is well supported in some recent studies by Robertson and his co-workers.[1]

The striking subjective improvement in these patients results of course from the sudden elimination of toxemia. The toxemia of pneumonia is a problem which we do not thoroughly understand. Coca[2] has demonstrated in filters of pneumococcus Type I cultures a

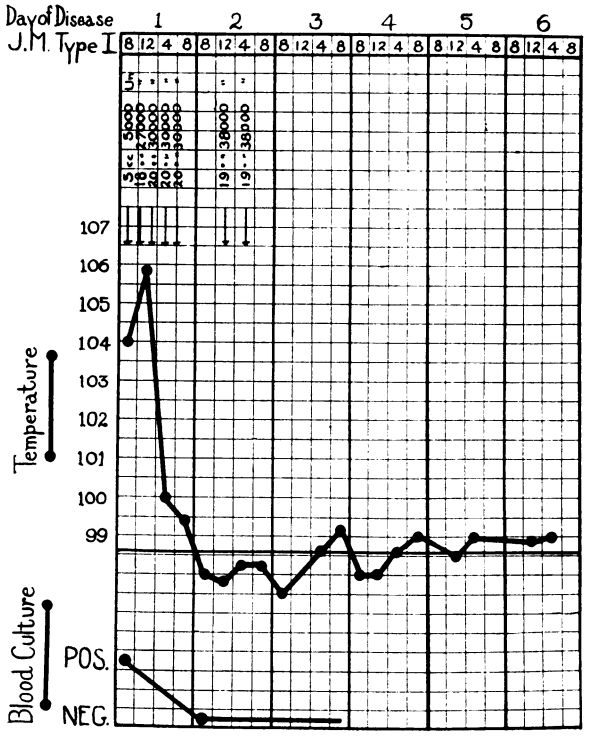

FIG. 1.
Septic Type I pneumonia treated on first day of disease with concentrated antipneumococcus serum. Upper line = temperature. Lower line = bacteremia.

toxin which, when injected into young children, causes a rise of temperature which may reach 105 in the more susceptible subjects. On the other hand, patients convalescing from pneumococcus pneumonia were found immune to the Type I toxin. According to Coca, the toxin appears to be type-specific, but is not the type-specific polysaccharide. If Coca's studies are corroborated, we may assume that antipneumococcus serum, in addition to neutralizing the type-specific polysaccharide, neutralizes the type-specific toxin as well. Certainly the crisis which accompanies abortive pneumonia, often on the second or third day of the disease, is just as dramatic as the natural crisis which occurs on the seventh or eighth day in those who receive no

serum. We can all recall acutely ill pneumonia patients who, on the morning after receiving serum, insist on telephoning their offices or reading the morning newspaper.

One of the most interesting methods of studying the effect of antipneumococcus serum on the pneumonic process is to take daily X-rays during the active period of the disease. By this method of study it can be shown that the prompt and adequate administration of serum usually limits the infection to one lobe. If serum is given very early, the area of infection in the involved lobe is sharply demarcated and rapidly fades out. When serum is started a little later, twenty-four to forty-eight hours after onset, it often happens, as pointed out by several observers, that though an immediate crisis is induced, the area of consolidation in the involved lobe increases somewhat in size and may even involve the entire lobe.

Numerous writers have stressed the value of antipneumococcus serum in preventing or checking bacteremia. Even when serum is given late in the disease, a heavy bloodstream infection is often overcome, though a fatal termination may ensue. When bacteremia develops early in the disease, it is promptly eliminated by serum therapy. This is well illustrated in Figure 1.

Figure 2 illustrates the effect of early serum therapy on bacteremia in two monkeys who were given lethal doses of pneumococcus Type I intratracheally.[3] Both animals rapidly developed the classic signs of lobar pneumonia accompanied by bacteremia. Pneumococci promptly disappeared from the bloodstream after the first injection of Type I antipneumococcus serum.

The mechanism of this phenomenon is fairly well understood. The pneumococci are apparently agglutinated by the serum and are filtered out of the blood as it passes through the liver and spleen.

One of the earliest reactions to pneumococcal infection of the lungs is a leukocytosis, preceded in some cases by a fleeting leukopenia. This leukocytosis is due almost entirely to an increase in the number of polymorphonuclearcytes. In man the total count is usually between fifteen and twenty-five thousand, with the polymorphonuclears ranging from 80 to 90 per cent. In exceptional cases the leukopenia persists, while in still others the count may go to forty thousand or more. In experimental animals, the same leukocytic response

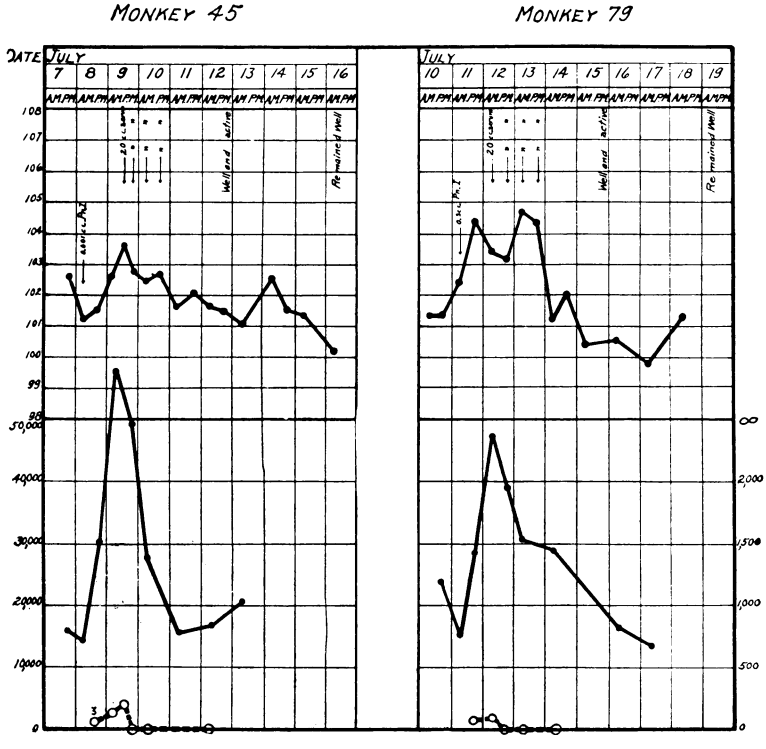

FIG. 2.

Abortive Type I pneumonia in monkeys produced by early and intensive serum therapy. Upper solid line = temperature. Lower solid line = leukocytes. Broken line = bacteremia.

is observed. In monkeys this leukocytic response is sometimes quite marked. (This is well illustrated in Figure 2.) Schilling counts reveal a sharp increase in the percentage of immature white cells in the blood. When antipneumococcus serum is administered early in the disease and localizes the pneumococcal infection in the lung, there is usually a prompt drop in the polymorphonuclears. With this drop there is an accompanying fall in the percentage of immature cells and a sharp increase in the number of monocytes.

Dochez[4] showed that at the time of the natural crisis in pneumonia, the so-called "protective bodies" first made their appearance in the circulating blood. In numerous instances during our studies at

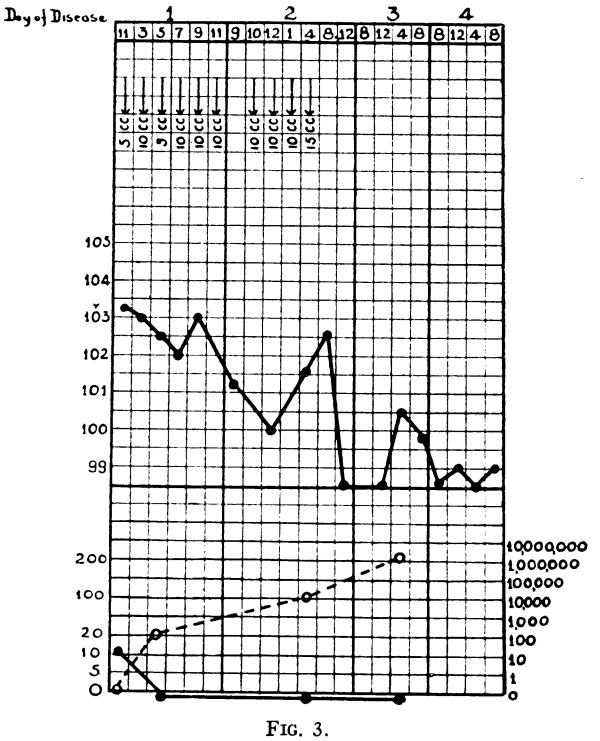

FIG. 3.

Septic Type I pneumonia in man treated during first 24 hours of disease with concentrated antipneumococcus serum. Upper solid line = temperature. Lower solid line = bacteremia. Dotted line = protective bodies in patient's serum.

Bellevue Hospital, we have demonstrated the prompt appearance of protective bodies in the serums of pneumonia patients who had been early and adequately treated with serum. (Figure 3.) Bullowa[5] has demonstrated homologous agglutinins in the blood of pneumonia patients after treatment with specific serum, and has made practical use of this test for determining when the patient has had a sufficient quantity of serum. The precipitins run parallel with the agglutinins and have the same significance. Protective bodies, agglutinins and precipitins all have a similar connotation, indicating that so far as humoral immunity is concerned, the patient has obtained control of the infection.

Tillett and Francis[6] were the first to show that when pneumococcus polysaccharides are injected intradermally into patients who are convalescing from pneumonia, they induce a cutaneous reaction in patients infected with the homologous type of pneumococcus. The character of this reaction is of the wheal or erythema type. The patient's capacity to react to the homologous polysaccharide is intimately associated with recovery and with the presence of type-specific antibodies in the circulating blood.

Francis[7] has recently shown that the polysaccharide skin test can be made use of as a valuable guide in serum therapy. In the opinion of Francis, a positive skin test inevitably denotes that recovery has begun. When negative it indicates the need of further serum therapy. Francis believes that the mechanism of the positive skin test is closely related to that operative in recovery from pneumonia, and is apparently a resultant of antibody and tissue activity. In Francis' illustrative charts, the appearance of a positive skin reaction was usually, but not always, coincidental with the appearance of specific agglutinins in the circulating blood. Both of these responses were closely associated with the critical fall in temperature and other evidences of recovery. Abernethy[8] has confirmed the value of the polysaccharide skin test in controlling serum therapy. He found that approximately two hundred thousand units was the amount required in treating the average uncomplicated case of Type I pneumonia.

In most case reports on the effect of treatment of Type I pneumonia with antipneumococcus serum, the death rate for patients treated during the first three or four days of the disease has averaged about ten per cent. In other words, a reduction to about one-third the standard death rate (30%). The opportunity to give serum to a patient with Type I pneumonia during the first twenty-four hours of the disease does not often present itself. This is most unfortunate, for as we shall presently show, the results obtained by such very early treatment are truly spectacular. With the rapid typing methods now in vogue, there is no reason why more pneumonia patients should not receive very early treatment. In order to determine more accurately the effects of very early serum therapy, the writer has collected a series of 160 cases of Type I pneumonia who received concentrated Type I serum *during the first twenty-four hours of the disease.*

Thirty-seven of these cases are from the author's own personal records. The remainder have been collected from the records of Bullowa,[5] Heffron[8] and Rogers.[9] In Table 1, I have summarized the data obtained from my own 37 cases. The average age in this series was 36; the average total dose of serum, 181 thousand units; the average duration for patients who recovered was 4.7 days. The latter figure is quite significant when we recall that the average duration for Type I pneumonias who receive no serum is seven days. In other words, the average duration of the disease was cut almost in half. In some of the cases, the temperature dropped to normal in less than forty-eight hours after onset.

TABLE 1.

SUMMARY OF CASES OF TYPE I PNEUMONIA WHO RECEIVED SERUM DURING FIRST 24 HOURS OF DISEASE.

Number of cases	37
Died	2 (5.4%)
Average age	36 years
Average duration	4.7 days
Average amount of serum	181 thousand units
Lobes involved: 1 lobe	78.4%
2 lobes	21.6%
Complications: Empyema	0
Acute parotitis	1
Other complications	0

In 78.4 per cent, these patients who received serum early had only one lobe infected. In 21.6 per cent, there was involvement of two lobes. There was no way of knowing whether both lobes were already involved at the time serum was given, or whether a spread took place after the injection of serum. This point could probably be settled by careful X-ray study of a series of cases.

The most interesting feature of this series of 37 cases was the practical absence of complications. When one recalls that more than six per cent of Type I pneumonias develop empyema, the complete absence of this complication in the present series is quite significant. Indeed, there were no complications of any kind in these patients, except one instance of acute parotitis.

There were only two deaths (5.4%), a remarkably low figure for such a serious disease. One of these deaths occurred in the group of

ten cases collected from the author's private practice. He was a man sixty years old, originally an alcoholic who later became a confirmed veronal addict. His general health was very poor at the time he had pneumonia. He received 150 thousand units of Type I serum.

The other fatality occurred in the group of 27 cases collected from our pneumonia records at Bellevue Hospital. The patient was 44 years old; also a chronic alcoholic. On admission his leukocyte count was only six thousand cells. For some reason, he received only 52 thousand units of Type I serum, not nearly enough for a patient who was obviously a poor risk. He died on the fourth day of the disease.

In Table 2, I have collected from sources mentioned above, 160 cases of Type I pneumonia who received serum during the first twenty-four hours of the disease. In this series there were 8 deaths, a mortality rate of only 5.0 per cent, one-third the death rate for *all* serum-treated cases, one-sixth the standard death rate for non-serum treated cases. These figures are certainly impressive, but no more so than the 25 cases of Type I pneumonia recently reported by Abernethy,[8] who were treated comparatively early with concentrated serum at the Hospital of the Rockefeller Institute. There was not a single death in Abernethy's series, and none of the patients developed empyema or other serious complications.

TABLE 2.

MORTALITY RATE FOR 104 CASES OF TYPE I PNEUMONIA WHO RECEIVED SERUM DURING FIRST 24 HOURS OF DISEASE.

Authors	Cases	Deaths	Per Cent
Cecil	37	2	5.4
Bullowa	13	0	0.0
Heffron	87	5	5.7
Rogers	23	1	4.3
Total	160	8	5.0
All serum*	1494	234	15.7
No serum*	565	190	33.6

*Cases collected from various authors.

Results such as these furnish much food for thought. Those of us who are interested in public health can now visualize the ultimate

control of pneumonia, for there is every reason to believe that what has already been accomplished with Type I serum can be achieved with the other types as well. It is true that Type III pneumonia presents certain difficulties, but figures are already at hand which show that Types II, V, VII, VIII and XIV are amenable to serum therapy. No doubt, in the course of time, investigators will be able to demonstrate for the other types of pneumonia what we can now prove for Type I, namely, that the early and adequate use of anti-pneumococcus serum reduces pneumonia to a comparatively mild infection.

Finally, when one considers that serum is now available for approximately 65 per cent of all pneumococcal pneumonias, he cannot fail to be impressed with the great gap which exists today between what *could* be done and what *is* being done for the pneumonia patient. Herein lies the reason for the campaign for the control of pneumonia which is now being conducted in New York State.

SUMMARY.

When patients with pneumococcus Type I pneumonia are treated early with homologous serum, the following phenomena are frequently observed:

1. The disease may be completely aborted, the temperature and the pulse and respiration rate dropping to normal within twelve to twenty-four hours after the administration of serum.
2. Striking improvement in the patient's general condition, due to the disappearance of toxemia.
3. Early serum treatment prevents the spread of infection from one lobe to another, and even limits the area of infection in the lobe primarily infected.
4. Bacteremia is prevented or, if already present, is quickly checked.
5. The leukocytes rapidly return to normal.
6. Homologous agglutinins, precipitins and protective bodies promptly make their appearance in the circulating blood.
7. Skin tests become positive to the homologous polysaccharid.
8. The death rate is cut to one-third or even one-sixth of the standard death rate for untreated Type I pneumonia.

9. These conclusions are derived from studies on Type I pneumonia, but evidence is rapidly accumulating that they apply with equal validity to several other types as well.

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DISCUSSION.

DR. THOMAS DARLINGTON (New York City): I was hopeful that Dr. Cecil would make quite clear that those statistics are at sea level and in hospital cases. I have had experience in mining camps where we had very few hospitals, and the death rate was very much higher, especially at high elevation. When I was at Tombstone, Arizona, in the neighboring camp there were seventy-seven cases and seventy-three deaths, but of course the elevation had a good deal to do with that.

DR. JABEZ H. ELLIOTT (Toronto, Canada): I should like to ask Dr. Cecil whether he has any proper control for the facts he has given us as to lowered mortality in using serum in pneumonia. He states that his best results are in the first twenty-four or forty-eight hours. He gives a death rate of patients dying with Type I pneumonia; I should like to know whether they were admitted

on the third, fourth, fifth, sixth, seventh, or eighth day, whether they were moribund, or whether there were complications. Can he give us any comparison of the death rates of patients treated with serum in the first twenty-four or forty-eight hours and of similar patients admitted to the hospital within the first twenty-four or forty-eight hours who have not been given serum?

DR. FRANCIS M. RACKEMANN (Boston, Mass.): There is one thing about Dr. Cecil's paper that I think deserves a little emphasis. That concerns what he said about skin tests. Obviously skin tests as a method of aid in diagnosis of acute and chronic infections are coming into their own. His figures illustrate one of the cardinal principles of skin tests, namely, that the immediate urticarial reaction is evidence of the later phase in the development of immunity because this reaction appears at the time antibodies appear, as Dr. Cecil pointed out. It is precisely the same thing that occurs with serum disease in a number of other conditions of this sort.

DR. RUSSELL L. CECIL (New York City): Figures were prepared several years ago on the death rate for quite a large number of cases admitted to Bellevue during the first forty-eight hours of the disease, and it was about 28 per cent, several points lower than for the group as a whole, though I do not think it affects the statistics to any marked degree.

I have not worked out the figures for the admissions during the first twenty-four hours. I think that is a good point and it should be done. I doubt if it makes much difference, though, in the standard death rate, because that has been done in a good many hospitals and it seems to run around 30 per cent. Outside, in private practice, of course, it would be lower, but I think that Type I pneumonias in hospitals will run a death rate of between 25 and 30 per cent, whether they are admitted on the first day or on the fifth or sixth day.