PRESENT STATUS OF SERUM THERAPY IN PNEUMONIA*

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IT IS interesting to compare the development of serum therapy for pneumonia with that of some other forms of specific therapy, such as diphtheria antitoxin for the treatment of diphtheria or insulin for the control of diabetes. In the two latter conditions the specific agents were produced in almost perfect form from the very beginning. Because of this perfection, the medical profession took hold of the new agents with much alacrity and enthusiasm and within a year after their introduction, diphtheria antitoxin and insulin were being widely used by physicians.

The serum therapy of pneumonia, on the other hand, has had a gradual evolution. There have been many obstacles to be overcome and considerable skepticism and indifference on the part of the medical profession to be combatted. The original Type I serum as produced by Cole[1] and his associates was applicable for only Type I pneumonia and, furthermore, the patient's sputum had to be typed by a laborious and time-consuming method before the serum could be administered.

The original Type I serum was bulky and had to be given in large quantities to be effective. As a result, inadequate amounts were often administered, and disappointing results were obtained. The large amount of horse protein in the serum caused severe serum sickness in many patients and the danger of anaphylactic shock and thermal reactions enhanced the unpopularity of the product. In spite of these drawbacks, however, the original Type I serum of Cole was an effective therapeutic agent. Its value was proven by the clinical and statistical evidence submitted by Cole and his co-workers,[1] and by the experimental studies of Cecil and Blake[2] on monkeys.

It has been just twenty-five years since the publication of the first articles on the use of Type I serum at the Hospital of the Rockefeller

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Institute.[1] It is therefore a fitting time to review briefly the advances which have been made in the serum therapy of pneumonia during the last quarter of a century.

First came the studies of Gay and Chickering,[3] Huntoon,[4] and finally the important investigations of Felton,[5] all of which showed that the specific antibodies in antipneumococcus serum could be separated by various chemical or biological procedures from the greater part of the protein content of the original serum. Felton[6] went still further and succeeded in concentrating antibodies until the refined and concentrated product contained five or ten times as much antibody per unit of volume as the original serum. The achievements of Felton simplified greatly the administration of serum and reduced considerably the incidence and severity of reactions.

This improvement in antipneumococcus serum was followed by extensive statistical studies by Cecil and his co-workers[7] at Bellevue Hospital, by Bullowa[8] at Harlem Hospital, and by Heffron,[9] and Sutliff and Finland[10] at the Boston City Hospital. The results obtained in these studies in city hospitals were not only impressive clinically but afforded convincing statistical evidence of the value of pneumococcus serum in Type I pneumonia. By using the alternate case method, it was shown that the death rate could be cut more than half by the use of serum. When only early cases were included, the fatality rate was reduced from the standard 30 per cent to less than 10 per cent.

The next important step in the development of antipneumococcus serum was the complete classification of pneumococci by Georgia Cooper and her co-workers.[11] A Type II antipneumococcus serum had already been tried with promising results, but with the demonstration of thirty odd types of pneumococci, the whole field of serum therapy in pneumonia was greatly widened.

It was fortunate that about this time Neufeld's[12] Quellung reaction was rediscovered and this led to a greatly simplified and accelerated method of typing pneumococci from the sputum and other body fluids. Whereas heretofore it had been necessary to inject a mouse with the sputum and then wait eight to twenty-four hours before testing the exudate, it was now possible by the Neufeld method to determine the type directly from fresh sputum within an hour or two after the sputum had been sent to the laboratory. This contribution has had a most important influence on the serum therapy of pneumonia, for even with

thirty odd specific antisera ready for administration to the pneumonia patient, much valuable time would be lost if we still had to determine the type by putting every sputum through the peritoneum of a white mouse.

One of the most recent advances in the specific therapy of pneumonia has been the introduction of antipneumococcal rabbit serum. This work also emanates from the Rockefeller Institute, and the first report in 1937 by Horsfall, Goodner and MacLeod,[13] created wide attention and interest.

At the present time both horse serum and rabbit serum are available for the treatment of pneumonia. It will probably take several years of comparative study and investigation before we can be sure which serum has the greater merit. Some workers believe that rabbit serum is distinctly preferable to horse serum; others believe that so long as the serum is highly potent, it makes little difference from what animal it is derived.

No serum should be used unless its potency is known. The strength of serum is measured in units "per cc.," the unit being that amount of antibody which will protect a white mouse against one million fatal doses of virulent homologous pneumococcus culture.

Antipneumococcus serum is usually dispensed in vials containing ten to twenty thousand units. Cloudy serum should not be used. At the present time in the City of New York, the Department of Health provides antipneumococcal horse serum for Types I, II, V, VII and VIII. Some of the biological manufacturers, however, are going further, and provide antipneumococcal rabbit serum for the less prevalent types, such as Types III, IV, VI, XIII, XIV, XVII and XIX.

I believe that every case of pneumonia from which a definite pneumococcus type is determined and for which there is an available serum, should have serum therapy. Even apparently mild infections should usually receive serum, not only because it shortens the disease, but because an apparently mild pneumonia may suddenly become a very severe pneumonia. The only contraindications to serum therapy are terminal pneumonias and marked allergic states. With two types of serum available, it will often be possible to circumvent an allergic condition by giving a serum to which the patient is not sensitive. In patients with very low blood pressure, intravenous injections of glucose and saline may be given before starting the serum. In any case, the physician should have a good reason for withholding serum, for he assumes considerable re-

sponsibility in so doing.

The use of antipneumococcal serum in the pneumonias of infants and children appears to be justifiable in many cases. I have had comparatively little experience with infantile pneumonia. However, C. H. Smith[14] at Bellevue Hospital and Bullowa[8] at Harlem Hospital have both reported excellent results with serum therapy in the types of pneumonia which are most frequently encountered in childhood, namely Types I, VI, XIV and XIX. In children the serum may be given intramuscularly or intravenously.

Tests for Sensitivity

No patient should be given antipneumococcus serum without careful inquiry as to the incidence of hay fever, asthma and urticaria. Patients should also be questioned concerning previous injections of serum. Asthma is not necessarily a contraindication to serum therapy, provided there is no sensitivity to the serum that is to be employed; but in administering serum to an asthmatic, the physician should proceed with great caution.

Intradermal Test. Once a decision has been reached to administer serum, the preliminary intradermal and conjunctival tests should be performed. For the intradermal test, two injections are made on the forearm at least two inches apart. The first contains a drop of 1:10 dilution of normal horse serum. The other, a small drop of physiological salt solution, serves as a control. In a positive reaction the wheal becomes larger and is surrounded by a zone of erythema. In a strongly positive reaction, pseudopodia are present. The conjunctival test is performed by inserting a drop or two of 1:10 dilution of normal horse serum in the conjunctival sac of one eye. In case of a positive reaction, the conjunctiva becomes injected and there is itching and watering of the eye. The readings for both tests should not be made for fifteen minutes after the injection of the serum. Antipneumococcus serum may be administered with caution in the presence of a weakly positive skin test. In the presence of a positive eye test, serum should be withheld.

Desensitization. In a highly sensitive patient, desensitization is almost impossible to achieve and should not be attempted without consultation. The writer can recall two cases in which it was tried with very nearly disastrous results. A temporarily refractory state may be produced by means of adrenalin, during which adequate doses of serum may often

be given. An injection of 0.5 to 1.0 cc. of adrenalin five to ten minutes before the serum is administered usually suffices. Small doses of well-diluted serum are given first in gradually increasing amounts before attempting the full therapeutic dose.

Occasionally during the administration of serum, a crop of urticarial wheals appear, with intense itching. In such a case, the serum should be promptly discontinued and adrenalin given subcutaneously. After a short while, the remaining dose of serum may be administered.

A somewhat different procedure has been recommended before administering rabbit serum. A preliminary intravenous test is made by injecting 0.1 cc. of the type-specific rabbit serum, diluted with 0.9 cc. of saline solution. The pulse and blood-pressure are taken before the injection and five minutes following it. It is claimed that if a patient is sensitive to rabbit serum, there will be a fall in the arterial blood-pressure of twenty or more mm. of mercury and an increase in the pulse rate of twenty or more beats per minute. In the presence of such a reaction, rabbit serum should not be administered.

Administration of Serum

If the sensitivity tests are negative, we proceed at once to the administration of serum. A syringe containing 1.0 cc. of adrenalin should first be prepared to meet any emergency that might develop during the injection of the serum.

It is customary to give a small intravenous injection of serum before giving the full therapeutic dose. The amount injected differs in different clinics; usually 1.0 cc. of serum, diluted with 9.0 cc. of saline is administered very slowly with constant attention to the color and pulse rate of the patient. Such a small dose of course has no therapeutic value but if the patient takes it without any reaction, the physician will have a good deal more confidence in giving the full dose. If after one hour there is no reaction to the preliminary injection, we proceed to give 10 to 20 cc. of serum intravenously depending on the potency of the agent. With the present concentration of serum it is possible to give the average complete dose of one hundred thousand units in three to four injections of serum. In bacteriemic cases, two hundred thousand units should be administered during the first twelve hours of treatment. On the morning after the injection of serum, patients who have been treated early usually show a striking improvement. The temperature and pulse rate will have

dropped to normal or almost normal and the whole appearance of the patient will have changed for the better. In cases in which marked improvement has not taken place within twenty-four hours after the injection of serum, the question will naturally be raised as to the accuracy of the typing. Unfortunately errors in typing are fairly common, though it must be added in defense of the bacteriologist that these mistakes often occur through no fault of technique. The first specimen of sputum may not contain the infecting type of pneumococcus at all; or it may yield two types of pneumococci, thus leaving the physician somewhat confused as to which type of serum to administer. Even in some correctly typed cases, however, little if any improvement will be noticed on the second day and it may be necessary to give more serum. This is particularly true in patients over forty-five years of age and in those with more than one lobe affected. It is also observed in cases where serum is started after the third day. In any case, serum should be continued until the temperature and pulse rate return to normal or until the intradermal or agglutination tests are definitely positive. The intradermal test and the agglutination tests are somewhat difficult to carry out unless the patient is in a hospital; and in the last analysis, neither is so dependable as the clinical condition of the patient.

An excellent rule to follow is to take a blood culture on every patient with pneumonia just before the administration of serum. The presence or absence of bacteriemia is of the greatest import so far as prognosis is concerned, and furthermore the dosage of serum is doubled in the presence of sepsis.

It is well to remember that when a lapse of several days has occurred since the administration of serum, the greatest caution must be observed if serum therapy is to be renewed. Otherwise a fatal anaphylaxis may occur.

In some clinics there is a tendency now to give the entire therapeutic dose of serum in one injection. This procedure has come into vogue since the introduction of rabbit serum. However, for the general practitioner, particularly in treating a patient in the home, it is a safer practice to divide the serum into several doses. There is also a tendency to give a larger dosage when using rabbit serum. Horsfall and his colleagues[13] at the Rockefeller Institute often give 250 thousand units of antibody with one injection of serum.

Serum Reactions

The various reactions to serum therapy are now familiar to most physicians. In the acute allergic reactions which appear during or shortly after administration, the patient becomes dyspneic, flushed and cyanotic; the pulse is rapid and weak and there is apprehension, tightness in the chest, and often a desire to urinate or defecate; in some cases there is also nausea and vomiting. In the occasional fatal reactions, the pulse becomes imperceptible and there is marked cyanosis followed by respiratory failure and death. Acute allergic reactions are promptly relieved by injections of 0.5 to 1.0 cc. of adrenalin administered subcutaneously and well rubbed in. It is not necessary to inject the adrenalin directly into the vein. Thermal reactions are not so common now as they were in the early days of serum therapy. Occasionally, however, the patient will have a chill an hour or so after the injection of the serum, followed by a rise of one to four degrees in temperature. Usually there is a rapid drop, followed by profuse perspiration, but occasionally the temperature remains high (107° to 108° F.) and the patient may go into a profound shock and stupor. In case of hyperpyrexia, cold packs and ice water enemas should be used together with emergency stimulation. Serum sickness is another form of serum reaction which is much less frequently seen now than formerly. The giant urticaria which so often followed serum in the early days is now a rare complication. Mild urticaria develops in 15 to 20 per cent of patients who receive the modern concentrated and refined forms of antipneumococcus serum.

Results of Treatment

The introduction of antipneumococcus serum has revolutionized the treatment of pneumonia. The use of serum not only reduces the fatality rate by more than one-half but, if given early, prevents bacteriemia and greatly shortens the duration of the disease. The results of serum therapy for the various types are shown in Table I.

These figures have been compiled from the statistics of a number of different observers. The largest series is naturally the Type I group, for which serum has been used for many years. The death rate is cut from 32.6 per cent for controls to 13.6 per cent for serum treated cases. The results of serum treatment in Type I pneumonia have been remarkably consistent. For example, Lord and Heffron[15] report 1043 cases of

TABLE I

FATALITY RATES FOR PNEUMOCOCCUS PNEUMONIA OF THE COMMONER TYPES, WITH AND WITHOUT SERUM* (HORSE SERUM ONLY)

Type of Pneumococcus	*Serum Treated*			*No Serum*		
	No. of Cases	*Deaths*	*Mortality Per Cent*	*No. of Cases*	*Deaths*	*Mortality Per Cent*
I	3136	429	13.6	558	182	32.6
II	964	302	31.3	967	424	43.8
V	139	35	25.1	516	187	36.2
VII	109	13	11.9	404	117	28.9
VIII	41	4	9.8	319	60	18.8
XIV	39	4	10.2	167	34	20.3
TOTAL	4428	787	17.7	2931	1004	34.2

TABLE II

FATALITY RATES FOR PNEUMOCOCCUS TYPES I & II TREATED WITHIN AND AFTER SEVENTY-TWO HOURS

Pneumococcus	*Cases Treated Within 72 hours of onset*			*Cases Treated 72 hours, or more, after onset*		
	No. Cases	*Deaths*	*Mortality Per Cent*	*No. Cases*	*Deaths*	*Mortality Per Cent*
Type I	844	79	9.3	979	170	17.3
II	62	10	16.1	40	16	40.0

TABLE III

RESULTS OF SERUM THERAPY IN BACTERIEMIC CASES OF PNEUMONIA

Pneumococcus	*Serum Treated*			*No Serum*		
	No. Cases	*Deaths*	*Mortality Per Cent*	*No. Cases*	*Deaths*	*Mortality Per Cent*
Type I	651	225	34.5	325	225	69.6
II	189	105	55.5	381	282	74.0
V	36	26	72.2	113	87	76.9
VII	13	2	15.4	71	61	85.9
VIII	15	5	33.3	126	57	45.2
TOTAL	904	363	42.2	1016	712	70.0

* The figures presented in Tables I, II and III have been compiled from the published statistics of various writers.

Type I pneumonia treated with serum with a death-rate of 13.9 per cent. Rogers[16] reports that in 1023 cases of Type I pneumonia, treated with serum during the first four days of the disease, the death rate was also 13.9 per cent! Even lower figures have been obtained by Cole[17] at the Rockefeller Institute and by Bullowa[8] at the Harlem Hospital. Cecil and Plummer[7] obtained a higher figure at Bellevue, where 410 Type I pneumonias that received specific therapy had a death rate of 17.6 per cent.

In Table I it will be noted that the fatality rates for the other prevalent types of pneumonia are also very favorably affected by serum therapy. The total for 4428 cases of pneumococcal pneumonia treated with specific serum yields a fatality rate of 17.7 per cent, compared with 34.2 per cent for 2931 cases that received no serum.

Both Type II and Type III pneumonia have offered considerable resistance to serum therapy, presumably because they are both severe forms of pneumonia and have a natural fatality rate of 40 to 50 per cent. Thanks to more potent serum, Type II is now being favorably affected by specific therapy, but Type II pneumonia should be very promptly treated and with large doses of serum. In Table II, we show the importance of administering serum early in the disease.

The fatality rates of serum-treated cases are distinctly lower for those patients treated within the first seventy-two hours than for patients treated seventy-two hours, or more, after the onset of the disease.

In bacteriemic cases, the death rates for all types of pneumococcal pneumonia are double or triple the usual figure but here again the value of serum therapy is well shown. In Table III, the results of serum in bacteriemic cases are shown for the five prevalent types.

The fatality rate for septic cases treated with serum is 42.2 per cent, compared with 70 per cent for the septic cases that received no serum.

Type III Pneumonia. Pneumococcus Type III pneumonia still presents a serious therapeutic problem and because of the disappointing results obtained with serum therapy, efforts have been made to control the disease by chemotherapy, or by a combination of serum therapy with chemotherapy. For example, Rosenthal,[18] Long and Bliss,[19] and Cooper, Gross and Mellon[20] have reported favorable results with sulfanilamide in white mice and rats infected with pneumococcus Type III.

Heintzelman[21] has recently reported a series of nine cases of pneumococcus Type III pneumonia treated with sulfanilamide, with a fatality rate of only 22 per cent. The series is too small, however, to be of

much significance. In the very interesting bone marrow studies of Osgood,[22] the author showed that Type I antipneumococcal serum was more effective against Type I pneumococcus than sulfanilamide. However, he then showed that sulfanilamide plus a given dose of antiserum was more effective than corresponding doses of antiserum alone. His results support the view that sulfanilamide renders the pneumococcus more vulnerable to bactericidal substances present in the serum. In view of these findings, it would seem that further observations on the combined effect of sulfanilamide and type-specific antipneumococcal serum are in order.

Because of the favorable results obtained with sulfanilamide in frank Streptococcus hemolyticus infections, it is natural that chemists should be striving to obtain some derivative of sulfanilamide which will exercise a similar specific effect on pneumococcal infections. Up to date, the most promising synthetic agent of this kind is that advocated by Whitby,[23] who observed that 2-(p-aminobenzene-sulphonamido) pyridine protects mice effectively against 10,000 lethal doses of Types I, VII and VIII. This drug is frequently referred to as Dagenan or M. & B. 693. Fleming,[24] working with the drug *in vitro*, noted that its effect was bacteriostatic rather than bactericidal. He found no deleterious effect from the drug on the leukocytes and further noted that the efficiency of the agent was enhanced in the presence of specific immune serum. He suggested that to obtain the best results, the patient should be given specific serum as well as M. & B. 693. The drug appears to be less toxic than sulfanilamide though, if kept up for any time, it frequently causes nausea and vomiting. Evans and Gaisford[25] have recently reported in the *Lancet*, 100 cases of pneumococcus pneumonia treated with M. & B. 693. A control series of 100 cases was observed at the same time. A fatality rate of only 8 per cent was observed in the treated cases, while that for the untreated cases was 27 per cent. The weakness in this report is that quite a large proportion of the cases treated were not typed. At the present time Dagenan (M-B 693) is being tried out clinically in a number of New York hospitals. In many cases the results have been quite striking but in certain other cases, especially those treated late, the drug has not prevented a fatal termination. Perhaps the ideal combination may eventually prove to be a combination of specific serum with chemotherapy. Under any circumstances Dagenan must be looked upon as an important and promising addition to our pneumonia therapy, though

obviously still in the experimental stage.

The writer wishes to say a final word about the treatment of pneumonia in private practice. In a recent study with E. A. Lawrence,[26] we analyzed 911 cases of pneumonia from the records of private practice with especial reference to the incidence and fatality rates for different types and the results of serum therapy. The data obtained from the private practice series were compared with well-established data based on records from the public wards of large city hospitals. The most significant facts brought out by this study were:

1. The generally higher age incidence of pneumonia in the well-to-do classes.

2. The high incidence of pneumococcus Type III pneumonia in private practice. This probably resulted from the higher age incidence of this group.

3. Inadequate bacteriological study of private cases. Less than half of the patients available for the study had been properly typed.

4. Only 60 per cent of the private pavilion patients with Type I pneumonia received Type I serum. In the consultation series, a higher proportion received serum but the results of serum therapy in both series were not so favorable as those obtained in the wards of large city hospitals. The fatality rate of 23.5 per cent for the entire series of 115 private cases of Type I pneumonia in which serum therapy was given is almost double that reported from various other sources and is not conspicuously lower than the standard fatality rate for Type I non-serum treated cases. A number of factors such as the higher age incidence, delay in administering serum, and inadequate dosage of serum are presumably responsible for this high figure. Pneumonia in private practice is not so mild as it has often been considered. In view of the proven value of serum therapy in pneumonia, the administration of serum should be part of the routine treatment in every case amenable to serum therapy, regardless of the social status of the patient.

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