Remarks

ON

THE SERUM TREATMENT OF PNEUMONIA *

BY

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Pneumonia is a generic term which is applicable to any form of bacterial infection of the lung, accompanied by consolidation. To-day the time at our disposal compels a limitation of discussion to one variety of pneumonia. We will therefore pass over the pneumonias caused by the streptococcus, staphylococcus, Friedländer bacillus, etc., and confine our remarks to the commonest and most important of all types—namely, pneumococcal pneumonia—and the present status of serum treatment for this particular form of the disease.

The serum treatment of pneumococcal pneumonia is complicated by the fact that there are so many specific biological types of pneumococci. Investigators have shown that these types are not only independent so far as agglutination and precipitation reactions are concerned, but that in animal experiments specific protection against one type confers practically no protection against another. This specificity of pneumococcal types is dependent upon certain polysaccharides which exist in the capsule of the pneumococcus. If by means of various procedures the capsule is removed from the pneumococcus, the type-specific qualities are lost. Indeed, Griffith¹ of Cambridge has shown that by certain artificial procedures one type of pneumococcus can be transformed into another. This real or apparent change of type presumably takes place because of chemical modifications in the polysaccharide substance in the capsule of the pneumococcus.

This problem of the multiplicity of pneumococcal types is considerably simplified by the fact that three of the biological types are responsible for the majority of pneumococcal pneumonias. At Bellevue Hospital in New York City, we² have found that in a series of 4,310 cases of pneumococcal pneumonia 66 per cent. fall into one or another of these three types (Table I), which are

TABLE I.—Incidence of *Pneumococcus* Types in Lobar Pneumonia of Adults Treated in Bellevue Hospital, 1920–30*

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	—

* This series does not include cases admitted during the season of 1925–6.

now universally referred to as Type I, Type II, and Type III. The figures in Table I agree fairly well with those from other institutions, and indicate that Type I pneumonia is the commonest, constituting almost one-third of all pneumococcal pneumonias. Type II pneumonia ranks second in frequency, comprising almost one-fourth of the total pneumococcal infections. Type III is less important, making up only 11.1 per cent. of the series. Formerly the remaining one-third of pneumococcal pneumonias were grouped together in a miscellaneous or waste-basket group and referred to collectively as Group IV or Type IV pneumonia. This miscellaneous group,

* Read in opening a discussion in the Section of Pharmacology and Therapeutics at the Centenary Meeting of the British Medical Association, London, 1932.

however, has recently been considerably reduced in size by the separation of twenty-nine additional pneumococcal types.³ Some of these have a fairly high incidence, approaching that of pneumococcus Type III. They are particularly common in children, in whom the original three types are comparatively infrequent.

From the facts just presented, it is obvious that if a large majority of pneumococcal pneumonias are to be treated successfully by a specific serum a number of different serums will have to be prepared. Biological manufacturers have found from experience that it is difficult to get a highly potent polyvalent serum for more than three different types of pneumococci.

MORTALITY RATE

The death rate of pneumococcal pneumonia varies considerably with the class of patient studied. The figure is lowest in private practice, somewhat higher in hospitals of the better class, and highest in large city hospitals. For instance, the following table (Table II) indicates the difference in death rates for the various types of pneumonia at the Rockefeller Hospital and at Bellevue Hospital, both in New York City. The Hospital of the Rockefeller Institute attracts the better class of patient, whereas patients in Bellevue Hospital are recruited very largely from the slums of the East Side. The difference in death rates at the two institutions is striking. It will be noticed also that in both series the mortality rates for Type I and Group IV pneumonia are considerably lower than those for Type II and Type III. In our experience Type II pneumonia is the most virulent of all, with a death rate at Bellevue Hospital of almost 50 per cent.

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

Pneumococcus	Rockefeller Hospital	Bellevue Hospital
Type I... ..	11.6*	28.2†
Type II	28.5	48.9
Type III	43.0	42.7
Group IV	12.8	31.3
Total	19.5	35.8

* Mostly serum-treated cases.
† None received serum.

In this connexion it is also interesting to inquire into the cause of death in pneumonia. For many years it was customary to assume that patients with pneumonia died of heart failure; but if this is true it is certainly not heart failure in the ordinary sense. The majority of these patients appear to die of vasomotor collapse. The pulse becomes small and rapid, the blood pressure sinks lower and lower, and the patient's skin is wet with perspiration. The picture is quite suggestive of surgical shock. This vasomotor disturbance in patients moribund with pneumonia is usually accompanied by a pneumococcal bacteraemia; indeed, in many patients the blood stream is loaded with pneumococci. In this respect, of course, pneumonia resembles other acute infections, which become much more serious when the bacteria break through the local barriers and invade the blood stream. We may say, then, that a fatal pneumonia is usually a septic pneumonia, and that this sepsis is accompanied by a vasomotor paralysis which eventually leads to death.

SIGNIFICANCE OF IMMUNE BODIES IN PNEUMOCOCCAL PNEUMONIA

Before proceeding to the actual details of serum treatment in pneumonia, a word should be said about the rationale of serum therapy in this infection. How does

antiserum actually affect the pneumococcus? In the first place, it is fairly clear that the reaction is not a toxin-antitoxin phenomenon such as that which occurs between the diphtheria toxin and antitoxin. The serum appears to act directly on the pneumococci themselves. On the other hand, the reaction is not in the nature of a bacteriolysis. Pneumococci grow readily in homologous anti-pneumococcus serum, but Stryker⁴ has found that when pneumococci are cultivated in homologous immune serum the organisms lose their virulence and no longer possess capsules. Furthermore, they are no longer specifically agglutinable, and are now readily engulfed by the leucocytes, whereas previously, in the encapsulated form, the leucocytes had refused to take them up. It has also been shown that anti-pneumococcus serum neutralizes the so-called soluble specific substance which is set free in cultures and in the animal body during the growth of pneumococci. This soluble substance, first described by Avery and his co-workers,⁵ is specific for each type of pneumococcus and is manufactured in the bacterial capsule. We may say, then, that although the nature of the antigen-antibody reaction in pneumococcal infections is not thoroughly understood, it appears certain that anti-pneumococcus serum acts on the micro-organism by changing in some way the physical or chemical constitution of the capsule.

It has been shown by Dochez⁶ and others that recovery in pneumonia is accompanied by the development in the blood of the patient of various immune bodies, such as agglutinins, precipitins, complement-fixing bodies, and the protective substance. These immune bodies make their appearance at about the time of crisis and persist in the blood of the convalescent patient for some time after recovery. The same immune bodies are present in anti-pneumococcus serum, and, when this serum is introduced into the veins of a patient with pneumonia, it tends to accelerate the appearance of the immune bodies in the patient's serum.

Summarizing: In the struggle between the pneumococcus and the human host septicaemia spells death, and the development of immune bodies recovery, for the patient. By the introduction of an excess of specific antibodies the physician attempts to sensitize or opsonize the pneumococci, and thus prepare them for phagocytosis and destruction by the leucocytes.

SOME RESULTS OF SERUM THERAPY IN PNEUMONIA

Following the original studies of Neufeld and Handel⁷ in Germany, Rufus Cole⁸ and his associates at the Rockefeller Institute undertook an extensive investigation of specific therapy in pneumonia about 1912. Horses were immunized against Type I pneumococci, and the serum of horses thus immunized was then injected intravenously into patients infected with Type I pneumonia. The doses of serum recommended by Cole were quite high—100 c.cm. intravenously every eight hours until the temperature dropped and the patient showed definite improvement. In Cole's⁹ series of 431 cases of Type I pneumonia treated with Type I serum the death rate was 10.2 per cent. The normal death rate for Type I pneumonia was assumed to be approximately 25 per cent., but no actual control series of untreated cases were studied at the Rockefeller Institute.

In 1920 Cecil and Blake¹⁰ found that in experimental pneumococcal Type I pneumonia in monkeys Type I serum in every case saved animals that had been injected intratracheally with lethal doses of Type I pneumococcus culture. Normal horse serum had no therapeutic effect on the infected monkeys. Goodner¹¹ has contributed additional evidence of the value of Type I serum in experimental pneumococcal infection in rabbits produced by intracutaneous injection of pneumococci. Rabbits that received lethal doses of pneumococcus Type I intracutaneously were readily saved by intravenous injections of Type I serum.

Clinically, the effect of specific serum in Type I pneumonia is often very striking, particularly when the serum is administered early in the disease. Within twenty-four hours the temperature, pulse, and respiration may drop from a high point to normal. Toxic symptoms vanish, and the patient's whole appearance changes. Perhaps the most significant of all the clinical effects is the prompt disappearance of pneumococci from the blood stream of septic patients, except, of course, where the bacteraemia is overwhelming.

SERUM SICKNESS AND ANAPHYLAXIS

Thus, statistical, experimental, and clinical evidence all point toward the therapeutic value of specific serum in Type I pneumonia. Certain difficulties, however, have been encountered in the practical administration of this serum in hospital and in general practice. The serum in the form developed by Cole is beneficial for only one type of pneumonia. The technical difficulties connected with the administration of large doses of unrefined horse serum militate strongly against its extensive use in small hospitals and in private practice. Finally, the unrefined horse serum frequently produces reactions in the patient. These reactions may be either allergic or thermal. The allergic reaction may be acute in the form of so-called anaphylactic shock, or it may show itself only as a serum sickness with fever, urticaria, general adenopathy, and pain and swelling of the joints. Allergic shock reactions can be almost entirely avoided if the possibility of hypersensitiveness to horse serum is eliminated before the patient is treated. Serum sickness, however, sometimes in a severe form, develops in a high percentage of patients who receive unrefined horse serum. Thermal reactions are fairly common, and come on about an hour after intravenous injection. They are characterized by a chill, increased cyanosis, rapid rise in temperature from one to three degrees, and a profuse sweat followed by rapid fall of temperature.

PREPARATION OF SERUM

In view of these disadvantages it is not surprising that the original form of Type I serum has failed to achieve the popularity which it deserves, and, furthermore, that as a result of these disadvantages biological chemists have attempted to refine and concentrate anti-pneumococcus serum and to extend the field of its usefulness from Type I infections only to various other types of pneumococcal infection. For example, Gay and Chickering¹² in 1915 found that by mixing immune serum with a solution of pneumococci of the same type a precipitate was formed which contained most of the protective substance of the serum. This could be dissolved in an alkaline medium, and a clear solution of antibodies obtained. In 1921 Huntoon¹³ modified this method, using washed pneumococci, and thus produced a therapeutic agent practically free from serum protein and fairly potent in protective substance against Type I and Type II pneumococcus. Huntoon's antibody solution was polyvalent, but its protective power against pneumococcus Type II pneumonia was not as high as against Type I. Huntoon's antibody solution was tried out on a large series of patients in our wards at Bellevue Hospital in 1920 and 1921.¹⁴ Quite a substantial cut in the death rate was noted in both Type I and Type II cases; similar results were obtained by Conner¹⁵ and others who experimented with this agent. The practical objection to Huntoon's solution was its tendency to produce severe chills and its lack of adequate potency.

FELTON'S CONCENTRATED SERUM

During the past eight years our interest has been focused on a refined and concentrated form of anti-pneumococcus serum devised by Lloyd Felton of Harvard University. Felton¹⁶ in 1924 found that practically all the protective substance could be removed from anti-pneumococcus serum by adding the serum to a large amount of distilled water. More recently he¹⁷ has combined the salting-out method of Avery with his own method to refine and concentrate anti-pneumococcus serum. Felton's actual technique^{16, 17} for preparing concentrated anti-pneumococcus serum is as follows:

Twenty per cent. anhydrous sodium sulphate is added to standard anti-pneumococcus serum and allowed to stand in an incubator at

37° C. from one to two hours until a precipitate forms. After filtration, the precipitate is dialysed in running water from five to seven days, viscous membranes being used for the dialysis. The content of the sac is then adjusted to a pH of from 4.6 to 4.8, at which point a second precipitate forms. This precipitate is removed, and the clear supernatant fluid containing immune bodies and some globulin and albumin is adjusted at a pH of 6.8 and diluted four or five times with cold distilled water. A white precipitate is thrown down, containing practically all the protective substance in the original serum. This precipitate dissolves readily in sodium chloride, is high in protective power, and is practically free from chill-producing substances.

Felton's serum is polyvalent, containing immune bodies against both Type I and Type II pneumococcus. The concentration of this serum varies somewhat with different lots. This inequality, however, is overcome by pooling serums from several immunized horses. The actual ratio of its potency to unconcentrated serum depends largely on the potency of the particular unconcentrated lot with which it is compared. In articles, however, published by Felton¹⁸ and by Goodner,¹¹ and in experiments conducted in our own laboratory,¹⁹ it has been shown that the average potency of Felton's serum is eight to twelve times that of the original unrefined product as prepared in the best biological laboratories. Felton¹⁸ has devised a "unit" method of standardizing anti-pneumococcus serum. The "unit of protection" he employs is that amount of serum which will protect mice against one million lethal doses of virulent pneumococci. According to his "unit" method, a wide variation in potency, ranging from 100 to 2,000 units per cubic centimetre, can be demonstrated in serums that have already passed the Hygienic Laboratory standard. In other words, the Hygienic Laboratory test is one that sets a minimum standard of potency but does not measure the extent by which the serum may exceed the standard in protective value.

At the outset of our work with Felton's serum¹⁹ we tested its therapeutic value on monkeys infected experimentally with pneumococcus Type I pneumonia. Four monkeys were given lethal doses of Type I pneumococcus culture intratracheally, and all four monkeys promptly developed pneumococcus Type I pneumonia. Twenty-four hours later three of the monkeys received injections of Type I serum. The three treated monkeys showed almost immediate signs of improvement and pneumococci disappeared from the blood stream of each. The fourth monkey did not receive any serum, and died on the third day with a heavy pneumococcal septicaemia.

Method of Administering Felton's Serum

At the present time our method of administering this serum is as follows: As soon as the diagnosis of lobar pneumonia has been made, steps are promptly instituted for the determination of the pneumococcus type. By making use of a combination of the original mouse method of sputum examination with the rapid methods of Krumwiede²⁰ and of Sabin,²¹ it is now possible to obtain the pneumococcus type in a high percentage of cases in from one to five hours.

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 c.cm. of this is injected into the peritoneal cavity of a mouse. The remainder of the sputum is typed by the Krumwiede method. If the test gives a positive reading, it is usually accurate. If it is negative or unsatisfactory, the Sabin microscopical 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 centimetre of this culture is then injected into the peritoneum of a mouse, and microscopical 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 c.cm. of blood from the patient's vein and to add 1 c.cm. to a tube of broth and 1 c.cm. to each of two pour-plates.

The present technique for administering Felton's serum is as follows:

The patient is first questioned as to previous injections of horse serum, and as to history of hay fever, asthma, or hives. An intradermal and a conjunctival test are then made with a one in ten dilution of normal horse serum. If after fifteen minutes these tests are both negative, 5 c.cm. of Felton's serum are slowly injected intravenously. If the patient shows no reaction to this first injection of serum, a second of 15 to 20 c.cm. is given intravenously from one to two hours later, and this dose is repeated every two to three hours until the patient has received approximately one hundred thousand units (equivalent usually to about 100 c.cm. of serum). The amount of serum administered on the following day is determined by the clinical condition of the patient. If his condition has improved and if his chart shows a decided drop in temperature, pulse rate, and respiration rate, the amount of serum administered is approximately one-half of that administered on the first day. If, on the other hand, the patient's condition is worse, or if it remains unchanged, the intensive treatment is continued. On the third day the same policy is pursued. If the patient's temperature is under 100° F., and if his condition is good, the general rule is to give one or possibly two 10 c.cm. injections to prevent relapse. We have found from experience that if any benefit is to result from serum treatment it is usually apparent after two or at least three days of treatment.

In our investigations^{19, 2} at Bellevue Hospital with Felton's serum the alternate case method was used—that is, every patient diagnosed as having lobar pneumonia was given a number. The patients with even numbers received serum. Those with odd numbers served as controls. This method of selecting patients for treatment produced comparative groups that were surprisingly similar in all essential respects. In the first 851 cases treated it seemed desirable to give Felton's serum to *all* types of pneumonia, in order to eliminate the possibility that the effect obtained was non-specific rather than specific in its nature. By giving serum to Type III and Group IV pneumonias we had a control on Type I and Type II cases which were being treated with a highly specific product. At the end of this series it was clear that the serum was having no beneficial effect except in the Type I and Type II groups. This is well brought out in Table III.

TABLE III.—Comparative Mortality Rates for Patients Treated with Serum and Untreated Controls; First Bellevue Series

Type	Treated with Serum			Untreated Controls		
	Cases	Deaths	Mortality per cent.	Cases	Deaths	Mortality per cent.
Type I	152	31	20.4	144	45	31.2
Type II	102	40	39.2	102	53	52.0
Other types	175	49	28.0	176	54	30.7

A substantial diminution of the death rate was noted in both the Type I and Type II groups, whereas the death rate was practically unaffected by serum therapy in the other types. In view of these results the alternate case method was continued, but serum was given only to alternate Type I and Type II cases.

SPECIFIC THERAPY IN TYPE I PNEUMONIA

Altogether 239 cases of pneumococcus Type I pneumonia have been treated with Felton's concentrated serum¹⁹ with a death rate of 20.1 per cent.; 234 alternate controls showed a death rate of 31.2 per cent. (Table IV). When

TABLE IV.—Mortality Rates for Patients with Type I Pneumonia Treated with Felton's Serum and Untreated Controls

	Treated with Serum			Untreated Controls		
	Cases	Deaths	Mortality per cent.	Cases	Deaths	Mortality per cent.
Total series	239	48	20.1	234	73	31.2
Admitted within 72 hours of onset	103	12	11.7	97	26	26.8

the serum was administered early in the disease the difference between the death rate in the treated and the control cases was even more striking. One hundred and three cases of Type I pneumonia treated with Felton's serum within seventy-two hours of onset showed a death rate of only 11.7 per cent., while ninety-seven controls admitted to the hospital within seventy-two hours of onset, but receiving no serum, had a mortality of 26.8 per cent. (Table IV).

Fig. 1 shows the temperature curve of a patient with Type I pneumonia who was treated early with Felton's

FIG. 1.—Pneumococcus Type I pneumonia treated on the first day of the disease with Felton's concentrated serum. Positive blood culture became negative after five injections of serum.

serum. Following the intravenous administration of serum the temperature dropped rapidly to normal, pneumococci disappeared from the blood stream, and immune bodies were promptly demonstrable in the patient's serum. The favourable results obtained in Type I pneumonia with Felton's serum at Bellevue Hospital are fully corroborated by the figures of other investigators. Their findings are summarized in Table V. It is interesting to note how

TABLE V.—The Results of other Investigators in the Treatment of Type I Pneumonia with Felton's Serum

	Treated with Serum			Untreated Controls		
	Cases	Deaths	Mortality per cent.	Cases	Deaths	Mortality per cent.
Park, Bullowa, and Rosenbluth ²⁴	109	18	16.5	105	33	31.4
Finland ²⁵	80	17	21.3	70	22	31.4
Sutliff and Finland ²⁴	28	7	25	31	10	32.2
Physicians to the Royal Infirmary, Edinburgh ²⁶	12	0	0	17	5	29.4
Armstrong and Johnson ²⁶	16	1	6.3	—	—	—
Baldwin, H. S. ²⁷	19	1	5.3	20	5	25
Total	264	44	16.6	243	75	30.9

closely the combined figures of other investigators approximate to our Bellevue figures. The death rate for 264 Type I infections treated with concentrated serum is slightly more than half that for 243 Type I cases who received no serum.

From all these figures it is clear that Type I pneumonia is amenable to serum treatment, and that the serum, especially when used early in the disease, produces a marked reduction in the death rate in this type of pneumonia. In my opinion it is doubtful whether the

mortality rate for Type I pneumonia in hospitals will ever be reduced below 10 per cent., as so many of the patients have, in addition to pneumonia, some chronic systemic or degenerative disease.

SERUM TREATMENT IN TYPE II PNEUMONIA

Of the various types of lobar pneumonia, pneumococcus Type II ranks second in frequency, being exceeded only by the Type I group. The death rate for Type II pneumonia at Bellevue Hospital is almost twice as high as for Type I. The mortality rate is closely related to the presence or absence of bacteraemia, and is furthermore dependent on the number of organisms present in the blood stream. The mortality for Type II pneumonia varies, as in all other types, with the age of the patient. Between the ages of 20 and 30 the death rate in our cases was only 22.2 per cent.; while in patients over 60 the mortality was 78.5 per cent. The seriousness of Type II pneumonia has stressed the need of some form of serum therapy for this type of the disease. Past efforts, however, to develop a serum for Type II infections have not been successful, and the reason for this failure is not hard to find. In the first place, according to Dochez and Avery,²⁸ a much greater amount of the so-called soluble substance is generated by Type II than by Type I pneumococcus. The Type II serum, to be efficient, must neutralize all this soluble substance in the blood stream, and must also eliminate from the blood the pneumococci which are usually present in severe infections. Such a situation calls for the administration of a highly potent serum early in the disease, but great difficulties have been encountered when one attempts to meet these requirements, since the serum produced by immunizing horses against pneumococcus Type II is much less potent than a good Type I serum. Cole,²⁹ for example, found that whereas the horse serum against Type I is of such a strength that 0.2 c.cm. will regularly protect a mouse against 0.1 c.cm. of virulent culture, it has been impossible to produce an immune Type II serum of any greater activity than that 0.2 c.cm. will protect a mouse against 0.01 c.cm. of culture. Manufacturers of biological serums, however, have improved the method of immunizing horses to such an extent that serums now prepared against Type II pneumococcus are of such a potency that 0.2 c.cm. will protect a mouse against 0.2 c.cm. of virulent culture, and when a serum of this potency is subjected to the concentration methods of Felton, a still more powerful product is produced.

STUDY OF ONE THOUSAND CASES OF TYPE II PNEUMONIA

During the past six or seven years we have been engaged in a clinical investigation of Type II pneumonia, and in the possibility of finding an efficient serum therapy for this form of the disease. Of the various products tested, Felton's refined and concentrated serum, either monovalent for Type II only or polyvalent for both Type I and Type II, has proved to be by far the most satisfactory product, not only because of its potency, but because reactions are only rarely produced by its injection. A few months ago Dr. Norman Plummer and I published a report² of this investigation, in which 1,000 cases of pneumococcus Type II pneumonia from the wards of Bellevue Hospital were subjected to clinical and bacteriological study, with special reference to the value of serum therapy.

The method of procedure was exactly the same as it was in the Type I study. The alternate case method was employed, even numbers receiving concentrated serum and odd numbers serving for controls. As in the case of Type I serum, the Type II refined product as prepared by Felton possessed a potency eight to ten times that of the original Type II serum. The method of administering the serum was also the same as that employed in the Type I series, with one exception. In view of the severity of the Type II infections, it seemed desirable to administer more serum to the Type II cases during the first twenty-four hours. Instead of 100,000 units, we try to approximate 200,000 units on the first day of treatment. The effect of Type II serum on the clinical course of Type II pneumonia 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 coincident improvement is rarely achieved. We have obtained a definite impression, however, that the symptoms of toxæmia are less pronounced in patients that receive serum than in those that receive none.

The crucial test of an anti-pneumococcal agent of any kind is its capacity to check pneumococcus bacteraemia. As stated above, a septic pneumonia is usually a fatal pneumonia, and, vice versa, a sterile blood culture is a favourable prognostic sign. Briefly, it may be stated that Felton's Type II serum has without doubt the capacity to sterilize the blood and to keep it sterile, provided, of course, that the sepsis is not extreme. In our series most of the early cases with beginning bacteraemia yielded a sterile blood culture the day after serum treatment was started. Fig. 2 shows the clinical course of one such

FIG. 2.—Pneumococcus Type II pneumonia treated on the second day of the disease with Felton's concentrated serum. Positive blood culture became negative after five injections of serum.

case. In this patient a definite therapeutic effect was quickly achieved by the prompt administration of serum, and pneumococci promptly disappeared from the blood stream. Even when sepsis is marked, as in some late cases of Type II pneumonia, large amounts of serum will often sterilize the blood, but this accomplishment may not prevent a fatal termination. For instance, in one of our cases plates showed innumerable colonies of Type II pneumococci in the blood on admission. Following large amounts of serum the blood culture became sterile and the patient improved, but eventually died eight months later from empyema and lung abscess.

The effect of concentrated Type II serum on the mortality rate of Type II pneumonia is indicated in Table VI. This series covers 505 cases and dates from 1924,

TABLE VI.—Mortality Rates for Patients with Type II Pneumonia Treated with Felton's Serum and Untreated Controls

Treated with Serum			Untreated Controls		
Cases	Deaths	Mortality per cent.	Cases	Deaths	Mortality per cent.
252	102	40.5	253	116	45.8

when we first began to work with Felton's serum in Type II infections. The difference in the death rates of treated and untreated series (40.5 per cent. *versus* 45.8 per cent.) is certainly not striking, though it is in favour of the serum-treated group. During the last two years we have limited serum treatment in Type II pneumonia to cases

admitted within seventy-two hours of onset. We had been convinced from previous experience that specific therapy, when administered late in Type II infections, was practically useless. When alternate cases have been treated early in the disease the results have been quite satisfactory. For example, in twenty-one patients with Type II pneumonia treated within seventy-two hours of onset three died, a mortality rate of 14.3 per cent.; whereas of twenty controls thirteen died, a mortality rate of 65 per cent. This, of course, is a small series of cases, but certainly the results are promising and lead to the belief that the prompt and intensive use of refined serum in Type II pneumonia may save a considerable number of lives.

In Table VII the results obtained with Felton's serum in Type II pneumonia are tabulated as reported from

TABLE VII.—The Results of other Investigators in the Treatment of Type II Pneumonia with Felton's Serum

	Treated with Serum			Untreated Controls		
	Cases	Deaths	Mortality per cent.	Cases	Deaths	Mortality per cent.
Park, Bullowa, and Rosenbluth ²³	56	13	23.2	61	18	29.5
Physicians to the Royal Infirmary, Edinburgh ²⁴	17	5	29.4	24	10	41.7
Armstrong and Johnson ²⁵	10	2	20	—	—	—
Baldwin, H. S. ²⁷	35	9	25.7	29	15	51.7
Total	118	29	24.6	114	43	37.7

other clinics. The death rate for the entire series of serum-treated cases—24.7 per cent.—is considerably lower than the rate—37.7 per cent.—for the untreated controls, and therefore places Type II serum therapy in a more favourable light than do our own figures.

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

SPECIFIC TREATMENT OF TYPE III PNEUMONIA

A few attempts have been made to treat Type III pneumonia with concentrated Type III serum. The results, however, have not been encouraging either clinically or statistically. No doubt one reason for the failure is the lack of potency of Type III serums, but there are deeper difficulties than this. Type III pneumonia will probably be successfully controlled by Avery's bacterial enzyme, though up to the present time Avery's investigations³⁰ have been confined to the study of pneumococcus Type III infections in mice and rabbits. In both these animals, however, injection of the bacterial enzyme eighteen to twenty-four hours after injection of the animal with a lethal dose of pneumococcus Type III culture has resulted in recovery of the animal in practically every instance. According to Avery,³¹ the enzyme probably acts by causing a rapid decomposition of the specific capsular polysaccharide. The bacteria, freed of their capsules, may then be taken up and destroyed by the phagocytic cells of the infected animal.

SERUM TREATMENT OF THE NEW TYPES

Since the reclassification of the original Group IV pneumococci into twenty-nine specific types, Park and his co-workers³² have been developing concentrated anti-pneumococcus serums for the more prevalent types. In some of these, such as Type VII, serum seems to have a definite effect. It is too soon, however, to speak with any conviction on this subject. The serum therapy of the newer types is a problem for the future.

SUMMARY

The statement is sometimes made that anti-pneumococcus serum, even in its present refined and concentrated form, is not the ideal specific agent for the treatment of pneumonia, and that eventually some more powerful

or more highly specific agent will take its place. That such an agent may be discovered is, of course, quite possible. The studies of Avery and his co-workers on the effect of certain bacterial enzymes on pneumococci open up a new and very promising field for the control of pneumococcal infections, but thus far the only enzyme which has been discovered is that which affects Type III pneumococcus. Others may eventually be isolated which will control both Type I and Type II infections, and even some of the less prevalent types. These further developments, however, may be far in the future. For the present we must be content with anti-pneumococcus serum for the treatment of both Type I and Type II infections. We have seen that concentrated serum has a striking clinical effect on Type I pneumonia, especially when it is administered early in the disease, and we have shown that by prompt and adequate administration of serum the death rate in early Type I infections can be reduced from 25 to 30 per cent. to approximately 10 per cent. When we remember that Type I pneumonia constitutes one-third of all pneumococcal infections, it must be acknowledged that this is quite an achievement in itself. In Type II pneumonia the results are not so impressive, but even in this difficult group definite clinical effects appear to be obtained when the serum is administered early in the disease.

Modern bacteriology, then, has one more victory to its credit. It has proven the existence of many specific biological types of pneumococci, and through recognition of these specific types immunologists are working out a specific serum treatment which promises a sharp curtailment in the death rate of pneumococcal pneumonia.

CONCLUSIONS

1. The three dominant types of pneumococci are responsible (in America) for two-thirds of all pneumococcal pneumonias.

2. Type I pneumococcus is the most highly parasitic of the types, causing one-third of all pneumococcal pneumonias. Type II ranks second, producing one-fourth of the total.

3. Both Type I and Type II pneumococcal infections of the lung are amenable to serum treatment. In Type I pneumonia the results of serum treatment are excellent. In Type II pneumonia the effect of serum, while not so striking as in Type I cases, is nevertheless definite.

4. The development of a refined, concentrated, and polyvalent anti-pneumococcus serum has reduced the serum therapy of pneumonia to a simple, practical, and valuable therapeutic measure.

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TREATMENT OF LOBAR PNEUMONIA BY ANTI-PNEUMOCOCCAL SERUM

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The results of a preliminary study of twenty-six cases of lobar pneumonia, treated with concentrated anti-pneumococcal serum during the winter of 1930-1, have been published already,¹ and the account which follows is to be regarded as supplementary to the earlier report. Further trial was made during the winter 1931-2, with the important addition that alternate cases were treated, as nearly as possible, in order of admission to hospital. Thus a control group was established by which results of treatment could be judged.

SCOPE OF THE INQUIRY

One hundred and sixty cases of primary pneumococcal lobar pneumonia in adults, aged 20 to 60, comprising fifty-four cases of Type I infection, forty-eight of Type II, three of Type III, and fifty-five nondescript ("Group IV") formed the clinical basis of the inquiry. Generally speaking, the illness was more severe in Types I, II, and III than in the nondescript infections. Equal numbers of men and women suffered from pneumonias due to unclassified strains; the proportion of males to females in Type I and also in Type II cases was 4 to 1. No case was treated later than the sixth day of illness. The average age of the patients in the treated and control groups was the same, as also the average day of the illness on admission to hospital. Patients dying within twenty-four hours of admission, whether treatment was begun or not, were omitted from the series.

The only satisfactory method of administering anti-pneumococcal serum is by the veins, requiring some dexterity and care when repeated inoculations have to be made. There is constitutional disturbance or shock in some patients after inoculation, and the concentrated serum is costly; for these reasons treatment is not lightly to be undertaken except in Type I and Type II pneumococcal pneumonias—approximately two-thirds of the cases—for which alone therapeutic serums are available. It follows, therefore, that, in the interests of the patient and of economy, the serological type of infecting pneumococcus must be rapidly determined prior to treatment. A simple method has been devised to meet this need.

DIRECT METHOD OF DETERMINING PNEUMOCOCCAL TYPE

It has been found that the type can be determined² in a few minutes by the simple process of mixing on a microscope slide the three standard diagnostic serums, Types I, II, and III, with a fleck of the sputum to be tested. The specimen is then examined with the dry lens (1/6 inch objective) and 4 ocular with substage condenser removed. The pneumococci, which are normally only just visible with this magnification, appear greatly