

# THE SERUM TREATMENT OF LOBAR PNEUMONIA

## A REPORT OF THE THERAPEUTIC TRIALS COMMITTEE OF THE MEDICAL RESEARCH COUNCIL

During the last three years the Medical Research Council have assisted an inquiry at different centres in Great Britain into the therapeutic value of specific sera for lobar pneumonia, following the great development of similar work in the United States. When the Council appointed a standing Therapeutic Trials Committee in 1931 the investigation was placed under the control of that committee, and the present report summarizes the evidence obtained.

The work has been laborious ; for it was little more than a critical testing for practical use of methods which were already in common knowledge, and it involved the close consideration of a very large number of cases of pneumonia. The Council wish to express their gratitude to the workers who so willingly undertook this prolonged study, and brought their results together for joint consideration.

Interest in the treatment of pneumonia has for many years been felt more keenly in Scotland, where the disease is perhaps more prevalent in the winter months, than in England. For evidence used in the present report the committee are indebted to workers in Aberdeen, Edinburgh, Glasgow, and London. The observations at Edinburgh were made by Professor D. Murray Lyon and the other physicians to the Royal Infirmary ; those at Aberdeen by Professor Stanley Davidson, Dr. J. B. Ewen, and Dr. R. J. Duthie, in the City Hospital, Woodend ; and those in London by Dr. R. R. Armstrong and Dr. R. Sleigh Johnson in various London County Council hospitals and also at St. Bartholomew's Hospital. The Glasgow inquiry under Dr. John Cowan, Dr. A. W. Harrington, and Dr. R. Cruickshank was developed independently with support from the Scottish branch of the British Red Cross Society, but permission has kindly been given for the use of their results. Separate reports have been, or will be, published independently by these various workers. The present summary expresses opinions agreed upon at all four centres. The practical conclusions are based directly on the evidence obtained there, but it will be evident to anyone familiar with American work that they are not widely dissimilar from those accepted in New York and Boston.

During the two winter seasons 1931-2 and 1932-3 a total of 773 cases of lobar pneumonia between the ages of 20 and 60 years were studied at Aberdeen, Edinburgh, and London. Of these, 530 belonged to either Type I or Type II, and 241 were treated by serum. The figures for Glasgow for 1930-3 were 602 cases from 20 to 60 years old, of which 434 belonged to Type I or II, and 107 were treated by serum. It will be noted from what follows that a large series of cases is required in order to demonstrate fairly any beneficial action of the serum.

### Typing of the Pneumococcus

This was generally done on the fresh sputum, selecting that which was of a glairy (rusty) "pneumococcal" appearance rather than purulent expectoration. Lung puncture was rarely used. Sputum up to twenty-four hours old may be employed, but it is less satisfactory and was never employed in the present series.

The rapid method recommended by Armstrong of immediate typing from the sputum itself on a microscope slide was employed tentatively. This offers great advantages, not only in speed, the test requiring less than half an hour, but still more in that it can be used in places which are not licensed for experiments on animals. But it may be unsatisfactory with the horse sera that are usually provided for type testing, and most workers are

agreed that a clear result under the microscope is more often obtained when rabbit sera are employed. The Glasgow observers, however, have compared the results with concentrated horse serum and with rabbit serum, and conclude that these are equally reliable, provided that the serum, whether of horse or rabbit, has an agglutinin titre of, say, 1 in 160 to 1 in 320.

In every instance in the present series, excepting a few of Dr. Armstrong's group, the final typing was recorded on the result of animal tests, Sabin's method of examining the peritoneal exudate four hours after inoculation into mice being generally used, and if that failed the examination being completed later when the mouse was dead or moribund. Whatever the method used, some special experience is required for accurate results, and it should be ascertained that the diagnostic sera are reliable. More than one specimen of sputum should be examined to confirm the type.

### Serum Used

The therapeutic antisera were those made for the market either by the Lederle Antitoxin Laboratories, or Messrs. Parke, Davis and Co., or Messrs. Burroughs Wellcome and Co. The Council and the investigators are indebted to these firms for special facilities given in the supply of the sera. Almost all the observations were made with concentrated serum, the power of which to protect mice had been measured in the American Felton units.

It is clearly desirable that any further evidence as to the value of anti-pneumococcal sera shall be based on dosage expressed in stable and generally accepted units. During the progress of this investigation, action to facilitate such uniformity of notation in this country has been taken by the Standards Department of the National Institute for Medical Research. Suitable anti-pneumococcal sera of both Types I and II have been dried and are preserved under conditions ensuring permanence, the value of each having been measured in terms of the Felton unit, unofficially current in the U.S.A., by comparison with samples supplied for this purpose by Dr. Felton himself. Of these provisional British standards, that for Type I serum has for some time been on regular issue to the manufacturers of anti-pneumococcal sera for sale in this country, and a similar distribution of the Type II standard will shortly follow. Pending an international decision, and subsequent official action, this voluntary distribution should ensure that data relating to the dosage of anti-pneumococcal sera from different sources should be strictly comparable both here and in America, where a similar voluntary adoption of the Felton units is effective.

The serum has been given intravenously in all the cases under review. Intramuscular injection was found by some workers to cause painful swelling, and has the theoretical disadvantage that the antibodies may not be absorbed into the circulation as quickly as is desirable.

The beneficial action of serum, which is so conclusively evident in mice, is believed to be sharply specific for each type of pneumococcal infection. American evidence on this point was accepted, and accordingly no attempt was made in this inquiry to learn whether the benefit produced in the human patient might not be equally well obtained by treatment with simple horse serum or with a non-specific type of antiserum.

The treatment with serum was begun as early as possible, though in some instances the patients were first allowed several hours' rest in hospital to recover from the exhaustion caused by transport. If the infecting pneumococcus could be typed without many hours' delay no serum was given until the answer enabled treatment to be started at once with the appropriate antiserum. Otherwise a preliminary dose of 20,000 units of Type I, together with 20,000 units of Type II, was given; and subsequent treatment adjusted to the proper serum or abandoned in accordance with the type of pneumococcus ultimately found. The routine injection of the single specific serum was usually 20,000 units repeated about every eight hours or at least twice in a day. If the patient showed no clinical improvement after forty-eight

hours' treatment with serum, it was generally found to be useless to continue with it. But some severe cases which were beginning to improve but had not yet reached safety received more prolonged treatment. The total dosage of serum varied from 50,000 to 120,000 units in different cases; Type II cases seemed on the whole to require a larger dosage than Type I. After the fifth day of the illness it was generally felt, though not proved, that serum had no further useful action.

Very few instances of immediately harmful reaction to the serum were ever observed either at Glasgow or at Aberdeen. When these occurred they took the form of slight dyspnoea with tachycardia; the dyspnoea was immediately relieved by adrenaline. In both winter seasons there were at Edinburgh and in London several instances of alarming, though not fatal, reactions to the first injection of a few batches of a mixed I and II serum. These ill-effects were rigors, or dyspnoea and increasing cyanosis, or general collapse with a feeble pulse. Such reactions were considered to be "toxic" rather than "anaphylactic," for they were seen in several patients treated with a particular batch of serum, rather than in an occasional sensitive individual; they were worse the larger the amount of serum injected, and they were not alleviated by adrenaline. When a particular batch of serum was once known to be clinically "safe," it could be used on any patient with no further precaution than that of slow injection into the vein.

Delayed serum reactions were rare and slight with the concentrated sera. During the recent winter Dr. Armstrong, in London, used an unconcentrated "Wellcome" serum of high titre, which was one-third less costly. This unconcentrated serum was also tried to a small extent at Glasgow. Neither it nor the concentrated "Wellcome" serum ever caused severe immediate reactions, but the use of the unconcentrated product was more frequently followed by late effects such as rashes, swollen joints, and pyrexia. The unconcentrated serum appeared to be as effective as the concentrated form in controlling the pneumonia, provided that the same number of Felton units were given.

Taking the market price of the concentrated serum as 30s. for a phial of 20,000 units, the treatment of an ordinary case of lobar pneumonia with 80,000 units would cost £6.

### Selection of Cases for Treatment

The good results of insulin on patients with diabetes or of liver treatment in pernicious anaemia are so constant that the trial of these remedies in a very few cases was enough to establish their value. With the antiserum treatment of lobar pneumonia the conditions are very different. The action of the serum is only that of a partial factor for good, and its influence may be overwhelmed by an infection that has been allowed several days to establish its dominance in the patient, or by other complicating factors that weaken the patient's resistance. In order to measure precisely what this partial benefit may be it would be necessary to take two groups of cases of identical severity and initial history and compare the sickness and the fatality in each, the one being treated with serum and the other serving as a control. But this is impracticable, for few cases, even of "Type I" lobar pneumonia, are quite alike, and a sufficient number of similar cases could never be got together under one observer and under similar conditions. Some American workers have sought to avoid this difficulty by using a special system of ratings for the various harmful features of the disease, thus expressing each patient's numerical value in reference to a common standard. Such differentiation seemed too intricate, and perhaps too much a matter of personal judgement, for the present inquiry. If a straightforward comparison of treated cases with controls, under the average conditions whereby patients succeed one another in the wards of a hospital, could not reveal any advantage for those treated by serum, then common sense would conclude that the use of this remedy should be disregarded in the routine

of practical medicine. The method consequently agreed upon for London, Edinburgh, and Aberdeen was that alternate cases of lobar pneumonia, taken simply in the order of their admission to hospital, should be used respectively for serum treatment and controls. So far as possible both were treated in the same wards and under the care of the same physicians. In the independent inquiry at Glasgow, however, the "serum" cases were treated in the Royal Infirmary, and a series of patients of the same social stratum, admitted during the same period to the Belvidere Isolation Hospital under the care of one physician, served as the control group. It is clear that there may be serious fallacies in any system which contrasts a group of serum-treated patients with a control group drawn from a different stratum of the population, or with a control group in a previous year, when the severity of the prevailing pneumonia might have been different.

Certain principles of selection were laid down so as to make the data derived from the centres homogeneous, and to exclude from the comparison patients in whom the serum could not be expected to have any effect. For the latter reason all patients admitted later than the fifth day of illness were excluded from the inquiry. Also all patients dying within twenty-four hours of admission to hospital were then taken out of the series, though the evident severity of their illness would not have prevented their inclusion at first, either in the control or in the serum group. No case of pneumonia complicated by other obvious disease, such as gross nephritis, advanced heart disease, diabetes, etc., was accepted for either group. All forms diagnosed as bronchopneumonia were also excluded. That these limitations were desirable was agreed upon by all the workers at a preliminary conference on the subject. It will be appreciated, however, that, with such restrictions, it was difficult in three years to obtain fully adequate data for statistical purposes; thus, to take the Aberdeen figures as an example, 450 patients with pneumonia were admitted to the City Hospital, Woodend, during the period under review, but with the agreed limitations the number was reduced to 188, of which seventy were Type I cases, giving a total of only thirty-five available for treatment with Type I serum.

Sex was disregarded, but the question of age was too important to be neglected. Table II from the present series illustrates afresh the well-known fact that the fatality of lobar pneumonia tends to be much greater over the age of 40 than in younger persons. The fortuitous inclusion of a few more elderly patients in one group than in the other might influence unfairly the final figures for comparison. It was therefore decided to omit from the series all patients under the age of 20 and over the age of 60, and to classify the remainder into broad age groups. It will be noted that this plan still left altogether unregulated the chance scatter of distribution of patients with severe or mild pneumonia into either the serum or control groups, and also of those admitted for treatment early or relatively late in the progress of the disease. It was thought better not to attempt a deliberate sorting of cases in respect of mildness or severity, but to trust that the distortion of chance scatter would become almost negligible in a fairly large number of cases. Reference to a possible influence of the "severity factor" on the results is, however, made later in the report.

### Statistics of Results

Subject to the criteria mentioned above, patients at London and Aberdeen were placed in the groups for serum treatment, or for control, alternately in the order of their admission to hospital without selection as to age or severity. At Edinburgh the same general rules and criteria were observed, and there was no selection of cases for serum treatment. But in some wards of the Royal Infirmary serum was not used throughout the whole period of the inquiry, and consequently the patients from these wards overload the number of controls. In the other wards the alternate case plan was maintained to the end. At Glasgow the alternate case plan was not

used, but patients in one hospital were treated with serum and those in another hospital served as controls. Hence it is only at Aberdeen and London that the serum-treated cases equal the control cases in number.

TABLE I.—Type Incidence in Lobar Pneumonia for Cases of the Special Series

	1931-2	1932-3	Totals
Aberdeen:	per cent.	per cent.	per cent.
Type I ... ..	26 = 29.2	44 = 44.4	70 = 37.0
" II ... ..	20 = 22.5	16 = 16.2	36 = 19.0
" III ... ..	17 = 19.1	6 = 6.1	23 = 12.0
Other types ... ..	26 = 29.2	33 = 33.3	59 = 32.0
	83	99	188
Edinburgh*:	per cent.	per cent.	per cent.
Type I ... ..	54 = 28.0	15 = 20.0	69 = 26.0
" II ... ..	88 = 45.5	51 = 68.0	139 = 52.0
" III ... ..	9 = 4.7	2 = 2.7	11 = 4.0
Other types ... ..	42 = 21.8	7 = 9.3	49 = 18.0
	193	75	268
London:	per cent.	per cent.	per cent.
Type I ... ..	54 = 33.7	88 = 55.0	142 = 45.0
" II ... ..	48 = 30.0	26 = 15.6	74 = 23.0
" III ... ..	3 = 1.9	0 = —	3 = 1.0
Other types ... ..	55 = 34.4	43 = 27.4	98 = 31.0
	160	157	317

Totals for 1930-3

Glasgow:	per cent.
Type I ... ..	205 = 34.0
" II ... ..	228 = 38.0
" III ... ..	22 = 4.0
Other types ... ..	145 = 24.0
	602

\* In this table the data from Edinburgh, though not from the other centres, include patients dying within twenty-four hours of admission to hospital: hence there are two more Type I and eight more Type II cases in this table than in Table III.

The variability of the type incidence from season to season and from place to place shows how epidemics of pneumonia may differ bacteriologically, but, on the basis of these and other published figures, it may be assumed that two-thirds of all cases of lobar pneumonia in Great Britain belong to types which are suitable for treatment by the sera now available.

That the fatality of lobar pneumonia is influenced by the type of infecting pneumococcus as well as by the age of the patient is confirmed by the following table for the Type I and Type II cases from the present series.

TABLE II.—Fatality in Different Age Groups for Cases Treated Without Serum

Totals for Aberdeen, Edinburgh, Glasgow, and London

	Ages: 20-60			20-30			30-40			40-50			50-60		
	Total	Lived	Died	Total	Lived	Died	Total	Lived	Died	Total	Lived	Died	Total	Lived	Died
Type I	301	256	45	119	111	8	105	88	17	52	37	15	25	20	5
	(15% died)			(6.7% died)			(16.2% died)			(28.8% died)			(20% died)		
Type II	305	223	82	116	94	22	78	56	22	74	47	27	37	26	11
	(25.9% died)			(18.9% died)			(28.2% died)			(36.5% died)			(29.7% died)		

Effects of Serum Treatment

These may be judged by considering changes—(a) in the fatality rate (Table III), and (b) in the duration of illness among survivors in the series.

TABLE III.—*Effects of Serum Treatment on Fatality*  
 TYPE I: Totals for the Four Centres

Age Group	Controls			Serum			
	Cases	Deaths	Fatality per cent.	Cases	Deaths	Fatality per cent.	Expected Deaths*
20 to 40 ...	24	25	11.2	140	8	5.7	16
40 to 60 ...	77	20	26.0	44	10	22.7	11
					18		27

TYPE I: Individual Centres.

Age Group	Controls		Serum			
	Cases	Deaths	Cases	Deaths	Expected Deaths Based on Local Controls	Expected Deaths Based on Controls for all Centres
<b>Aberdeen:</b>						
20 to 40 ...	22	3	25	1	3	3
40 to 60 ...	13	6	10	0	5	3
				1	8	6
<b>London:</b>						
20 to 40 ...	47	2	58	5	2	6
40 to 60 ...	23	6	14	6	4	4
				11	6	10
<b>Edinburgh:</b>						
20 to 40 ...	31	5	19	1	3	2
40 to 60 ...	9	2	5	1	1	1
				2	4	3
<b>Glasgow:</b>						
20 to 40 ...	121	15	38	1	5	4
40 to 60 ...	32	6	15	3	3	3
				4	8	7

TYPE II: Totals for the Four Centres.

Age Group	Controls			Serum			
	Cases	Deaths	Fatality per cent.	Cases	Deaths	Fatality per cent.	Expected Deaths*
20 to 40 ...	194	44	22.7	111	14	12.6	25
40 to 60 ...	111	38	34.2	53	19	35.8	18
					33		43

TYPE II: Individual Centres.

Age Group	Controls		Serum			
	Cases	Deaths	Cases	Deaths	Expected Deaths Based on Local Controls	Expected Deaths Based on Controls for all Centres
<b>Aberdeen:</b>						
20 to 40 ...	13	3	15	2	3	4
40 to 60 ...	4	2	4	1	2	1
				3	5	5
<b>London:</b>						
20 to 40 ...	22	6	25	3	7	6
40 to 60 ...	15	1	12	1	1	4
				4	8	10
<b>Edinburgh:</b>						
20 to 40 ...	45	11	38	8	9	9
40 to 60 ...	32	11	16	5	5	5
				13	14	14
<b>Glasgow:</b>						
20 to 40 ...	114	24	33	1	7	7
40 to 60 ...	60	24	21	12	8	7
				13	15	14

\* The "expected deaths" are those which would have been recorded if the serum-treated groups had died at the same percentage rates as the corresponding controls.

From the combined figures from the four centres it would appear that serum treatment is capable of reducing the fatality from Type I and Type II pneumonia, but that the improvement is limited to patients under the age of 40. It is unfortunate, from the point of view of statistical analysis, that the number of patients over the age of 40 who were available for treatment was so much smaller than the number of younger patients. Nevertheless, on this evidence, it would seem that the life-saving effects of serum treatment are mainly, if not wholly, restricted to the ages at which natural resistance to the disease is ordinarily high. Looked at broadly the results do show a favourable influence on the fatality rate in the younger patients with Type I and also with Type II antisera. But a closer inspection of the separate results from each centre reveals anomalies that demand further analysis.

Aberdeen showed a fatality rate in Type I pneumonia which was reduced with serum from the expected figure of six to only one in thirty-five cases. London, on the other hand, found the fatality rate in Type I slightly increased with serum, whereas that in Type II was reduced to four from the expected figure of ten deaths. The aggregate London figures are the more surprising, because Dr. Armstrong himself had in his first winter's experience been vividly impressed by the benefit obtained with serum in Type I cases, and it was contrary to all his expectations when the figures of the second year swung the balance away in the opposite direction. In commenting on the change he observed that eighteen of his treated Type I cases were clinically classified as "severe," compared with only seven "severe" cases among his controls. This raised the question of the chance scatter of patients with poorer prognosis from any cause into either the serum or the control group preponderantly. But the case records at the other centres were carefully revised from this point of view, and there was no evidence of the control groups having been unduly weighted by the chance occurrence of severe cases among them.

Apart from clinical judgement, the severity of an individual case may be estimated by the results of blood culture and by measuring the leucocytosis. The latter method was used in routine examination at Aberdeen and Glasgow, though not at the other two centres. An initial leucocytosis below 15,000 per c.mm. carries a relatively unfavourable prognosis. Examination of the records from Aberdeen shows that on the whole the initial leucocyte counts were higher in the cases which happened to be treated with serum than in the controls, but there was no great inequality in this respect. Nor was the explanation to be found in an unequal incidence of early bacteraemia. Table V indicates that there were as many cases of early bacteraemia in the serum as in the control groups. The variation in the results at the different centres cannot be explained, but they show the difficulties in the way of accurately evaluating a treatment of this nature on the basis of small numbers of cases.

### Bacteraemia

At Aberdeen blood cultures were systematically taken throughout the inquiry; they were made on every patient and early after admission, but only once. Positive blood cultures were obtained in nineteen out of sixty-six consecutive cases (28.8 per cent.) by the method finally adopted of withdrawing blood by a syringe and injecting it directly into glucose broth. The earlier technique of using citrated blood in "venule" tubes for transference to broth gave a lower proportion of positive results. At Glasgow blood cultures were taken from all but twelve of the serum cases, and from 138 consecutive controls between the ages of 20 and 60; the cultures were made as soon as possible after admission, and the method of directly injecting the blood into glucose broth was adopted throughout. Table IV gives the total figures submitted from these two centres without distinction between the early and later methods of culture used at Aberdeen.

It would appear from the results shown in the table that serum treatment has little influence on the total fatality rates of cases with bacteraemia.

TABLE IV.—Incidence of Bacteraemia in Type I and Type II Cases (Serum and Controls) at Aberdeen and Glasgow

Type	Serum					Controls				
	Cases Examined	Positive	Deaths	Negative	Deaths	Cases Examined	Positive	Deaths	Negative	Deaths
I	84	28	5 (17.9% of positive cases)	56	0	95	23	4 (17.4% of positive cases)	72	11
II	65	18	7 (38.9% of positive cases)	47	7	95	22	11 (50% of positive cases)	73	8

### Effect of Serum Treatment on Duration of Illness in the Surviving Cases

Here, if anywhere, it should be possible to show clearly the favourable action of antiserum. In a series of one hundred patients there may be twenty so heavily infected that they would normally die, and only a few of these twenty are in a state where reprieve from death is possible by the use of serum. The eighty potential survivors must all be patients with less severe infection: they are mostly well inside the zone at the edge of which serum could just show its efficiency by saving a few cases from death. It is helpful to visualize this by a rectangular diagram in which a black area shows the 20 per cent. of massive and fatal infection, while the remaining 80 per cent. of progressively lighter tint includes all those in whom the infection was below the intensity needed to kill. Antiserum may push the black band a little further back, to 15 per cent. or less, and then it meets a final barrier. But through all the great area of survival cases it should also be effective in lightening the grey tint of illness.

There has been too little attention given to the action of serum on surviving cases. This is partly because it is less easy to make an exact analysis of such clinical improvement than to record the simple fact of death or survival; and partly because physicians are chiefly concerned with the hope of saving the life of a patient with pneumonia, knowing that if only this can be achieved convalescence is usually rapid, whether the pneumonia had been severe or mild. But the survivors offer for study a field where the effect of the serum should be more easily demonstrable, since they are presumably in that state of relatively light infection where the serum can act to full advantage.

At all four centres the experience was alike—namely, that the serum treatment of Type I and also of Type II cases lessened the duration of the fever and diminished the number of cases in which fever ended irregularly by lysis.

*Aberdeen* reported:

Type I pneumonia; average time of crisis:

In serum-treated cases, 33.8 hours after admission to hospital.  
In control cases, 101 hours after admission to hospital.

Type II pneumonia; average time of crisis:

In serum-treated cases, 36.6 hours after admission to hospital.  
In control cases, 104 hours after admission to hospital.

Edinburgh and Glasgow used a different measure for the recovery, but the improvement was equally evident. The percentages of cases in which the fever ended on or before the fifth day of the disease, disregarding time of admission to hospital, were:

*Edinburgh*:

Type I pneumonia: serum-treated, 36.4 per cent.; control, 8.3 per cent.

Type II pneumonia: serum-treated, 34.2 per cent.; control, 10.9 per cent.

*Glasgow*:

Type I pneumonia: serum-treated, 72.1 per cent.; control, 9.9 per cent.

Type II pneumonia: serum-treated, 34.1 per cent.; control, 5.3 per cent.

Dr. Armstrong in London found that the time of crisis occurred on the average two and a half days earlier in the illness in his serum-treated Type I cases, and two days earlier in his serum-treated Type II cases, than in the controls. The Glasgow workers also found that the average times of crisis in the serum-treated Type I and Type II cases were respectively two and a half and two days earlier than in the corresponding controls. Dr. Armstrong's table may be quoted in full, because it illustrates this clinical improvement in the survivors, despite a failure to influence the death rate in Type I cases (Table V).

TABLE V.—*Effect of Serum Treatment on the Course of the Illness in Survivors (London)*

	Type I				Type II			
	Treated		Control		Treated		Control	
	Cases	Av. day	Cases	Av. day	Cases	Av. day	Cases	Av. day
Crisis ... ..	47	4 $\frac{3}{4}$	35	7 $\frac{1}{4}$	26	4 $\frac{1}{2}$	19	6 $\frac{1}{2}$
Lysis ... ..	12	7	26	9 $\frac{1}{2}$	7	7 $\frac{1}{2}$	11	9 $\frac{1}{2}$
Continued fever ...	2	—	1	—	0	—	0	—

Data with regard to the convalescence were generally unreliable, because most of the patients were granted a routine time for recovery, and often a holiday before they were advised to resume full work.

In view of its effect on the course of the illness in Type I and Type II pneumonia, it might be expected that serum treatment would lessen the incidence of complications in patients who recovered from the initial infection. The total numbers of individual complications in both the serum-treated and the control groups at the four centres were, however, too small to enable fair comparisons to be made, except in the case of the important local complication empyema. There was a suggestion from the total figures that the liability to this complication was reduced by serum treatment in both Type I and Type II pneumonia. The figures submitted from the four centres showed that empyema occurred in four serum-treated Type I cases, against an "expected" figure of nine, and in one serum-treated Type II case, against an "expected" figure of three; in each case the expected figure was calculated from the incidence of empyema in the corresponding control group. The percentage incidence of this complication in the serum-treated and control groups for Type I and Type II pneumonia was as follows:

Type I: serum-treated, 2.4 (166 cases); control, 5.5 (256 cases).

Type II: serum-treated, 0.8 (131 cases); control, 2.7 (223 cases).

The evidence of the inquiry at the four centres is therefore in favour of the serum treatment, although with certain limitations. The inconveniences to the patient are little more than those of repeated intravenous injections. Fatality was reduced in the younger patients in this series by roughly half of the expected deaths. Thus in 140 serum-treated cases, aged 20 to 40, of Type I pneumonia there were eight deaths instead of the expected sixteen; and in 111 serum-treated cases of Type II there were fourteen deaths instead of the expected twenty-five. Also, the duration of illness among survivors tended to be shortened by from two to three days, curtailing just that period near the end of a pneumonia where anxiety grows as the fever persists; and was a suggestion that the incidence of empyema was lessened by giving serum. These benefits were obtained with both Type I and Type II cases of lobar pneumonia. On the other hand, the data obtained in this investigation suggest that serum treatment has little or no power to decrease the fatality from Type I or Type II lobar pneumonia in patients over 40, or in the severely ill cases with bacteraemia.

On clinical impressions the workers were all agreed that the appropriate antiserum frequently produces striking symptomatic benefit in cases of Type I and Type II lobar pneumonia, and that the best results are obtained with very early treatment. There was a con-

sensus of opinion at the four centres that it is probably useless to give serum later than the fifth day of the disease.

### Summary

1. Concentrated antiserum for Type I pneumococcus reduced the fatality in Type I cases of lobar pneumonia in adults between the ages of 20 and 40; from the total figures of the present inquiry, however, the treatment appeared to have little, if any, effect on the fatality in older patients (aged 40 to 60). The treatment seemed definitely to reduce the average duration of fever and illness in patients who recovered, and there was a suggestion that it also decreased the liability to empyema among survivors.

2. Similar effects were seen when Type II antiserum was used for cases of Type II lobar pneumonia.

3. Immediate serum reactions of a dangerous nature were rarely seen in the present series of cases, except that one or two batches of a particular concentrated mixed serum did cause rigors and collapse at both the centres where they were used. There were no unpleasant late anaphylactic results with the concentrated serum. On the whole, a good serum seemed to be devoid of disturbing effects on the patient, and on these grounds there need be no hesitation in the use of the treatment.

4. The benefits from serum are not so emphatic as to make it desirable that *all* severe cases of lobar pneumonia, irrespective of the type of the infecting pneumococcus, should be treated with Type I and Type II antiserum on the chance that they might belong to a type which is favourably influenced. Moreover, the special technique required for repeated intravenous injections, and the cost of the serum, make the treatment unsuitable for universal application. Each case must be typed as soon as possible, so that the appropriate serum may be used in the optimum dose; the use of the serum is not recommended except under conditions where typing of the pneumococcus can be obtained.

5. If accurate typing of the sputum can be done in five or six hours, serum should be withheld until the type is known, and then a dose of 20,000 Felton units of the specific serum given. But if more time is required for the typing, then a preliminary dose of 20,000 Felton units Type I, together with 20,000 units Type II, should be given, and the specific type serum, either I or II alone, continued when the nature of the infection is known. Treatment is continued by injection of 20,000 units at a time, twice a day, with approximately an eight-hour interval. Usually a total dosage of 80,000 units, with variation from 50,000 to 120,000 units, of the single specific serum is required, Type II cases, on the whole, needing a larger dosage than Type I. If no obvious clinical improvement occurs in the first forty-eight hours of serum treatment it is probably useless to continue with it.

6. The serum should be given intravenously. There is no satisfactory preliminary test for any peculiar sensitiveness of the patient to horse serum. The first injection should therefore be made cautiously and slowly, 1 c.cm. being introduced into the vein in a minute or two, and the total being injected in ten or fifteen minutes. Adrenaline solution 1 in 1,000 must be ready beforehand, and 1/2 or 1 c.cm. of this should at once be injected *subcutaneously* if the patient reacts unfavourably with collapse and failure of the pulse or urgent dyspnoea. Second and subsequent injections of serum may be given with less precaution. In addition to anaphylactic sensitiveness of the individual, there is the chance that the serum supplied by the manufacturer may contain protein substances which are toxic to most individuals, as occurred in a few batches used in the present inquiry. To safeguard against this, 1 c.cm. of the serum may be injected intravenously, and the remainder of the dose slowly injected half an hour later, provided that no untoward symptoms have occurred. This precaution is unnecessary if the batch of serum is known to be harmless, either from other experience or because the manufacturers state that it has already been tested from this point of view.

7. No data were collected in this inquiry with regard to the use of the serum in children, or in patients over the age of 60, or in cases of bronchopneumonia.