THE RELATION OF CIRCULATING ANTIPNEUMOCOCCAL IMMUNE SUBSTANCES TO THE COURSE OF LOBAR PNEUMONIA

III. INJECTED IMMUNE SUBSTANCES (ANTIPNEUMOCOCCUS SERUM, TYPES I AND II)

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In the consideration of this phase of the subject more attention will be given to certain objective changes occurring after the introduction of immune serum than to mortality. Our series of cases is far too small to permit any conclusions concerning the influence of serum therapy on the outcome of the disease. Mortality percentages will be taken into account in the discussion of the reports of other workers. We wish to present the data which we have secured from a study of the effect of immune serum, chiefly Type I, on the spread of the pneumonic lesion, bacteremia, the duration of the disease and resolution of the consolidated lung.

MATERIALS AND METHODS

The therapeutic antipneumococcus serum, Type I, was obtained from two different sources; one, the New York State Board of Health Laboratories,[1] the other, Lederle and Co. Both sera were of high potency; the concentrated antibody solution, Types I and II (Felton's Method) was secured from Lederle and Co. The dosage of unconcentrated serum employed was that recommended by Cole (1); namely 100 cc. every eight hours until the temperature fell and remained below 39° C. In the administration of the antibody solution we were guided by the recommendation of Cecil and Sutliff (2) that 80,000 to 100,000 units be given within the first twenty-four hours of treatment. The dosage thereafter depended on the changes in the temperature, pulse and respiration. If no improvement was manifest, the dosage was continued for another twenty-four

[1] Through the kindness of Dr. A. B. Wadsworth we were supplied with serum free of charge for the part of the study carried on at the Peiping Union Medical College.

hours. With improvement, the amount of antibody solution was reduced, and usually discontinued during the ensuing twenty-four or forty-eight hours.

Pneumococcidal tests were carried out exactly as in the preceding section on the study of acquired immune substances. An x-ray was taken, in so far as possible, immediately before the first dose of serum and thereafter at twenty-four hour intervals.

Clinical cases

The data on which the present study is based were secured from observations on twenty-nine cases of lobar pneumonia treated with serum. Of these, all except three were caused by Pneumococcus Type I. The observations on ten patients of the series were carried out at the Peiping Union Medical College and the Hospital of the Rockefeller Institute. The remaining nineteen were studied in the University of Chicago Clinics. A summary of all the findings pertinent to this presentation is shown in Table I.

Occurrence of pneumococcidal-promoting properties in the serum following injection of immune serum

In only one case of the twenty-nine did the patients' serum show any acquired immune activity before the institution of serum therapy. (Table I, Case 25, L. W. P.) After the first twenty-four hours of serum therapy, well marked pneumococcidal-promoting activity was demonstrable in the blood of every patient. The titer of the serum was frequently higher than that commonly observed in patients recovering spontaneously from the disease. With the further administration of the immune serum, the antipneumococcal activity of the patients' serum was maintained or increased. However, following discontinuance of serum therapy there was often a sharp decline in the pneumococcidal-promoting effect of the serum and not infrequently it completely disappeared from the patients' blood within a relatively short time (Chart II). More frequently a gradual diminution in the pneumococcidal-promoting activity occurred over a period of several weeks. As might be expected there was no definite relationship noted between the amount of immune serum given and the degree of pneumococcidal-promoting activity detectable in the patients serum even when rate of administration and stage of the disease were taken into account (Tables I and II).

Effect of immune serum on the spread of the pulmonary lesion

Definite spread of the pulmonary process was detected in only two cases subsequent to the first twenty-four hours of serum therapy. One patient, Number 1 (J. T. A.) (see Table I), showed fresh involvement of an

TABLE I

Relation of injected immune substances to course of disease

Case number	Type	Day of disease immune serum treatment begun	Amount of immune serum injected†		Titer of pneumococcidal-promoting activity of patient's serum		Spread of lesion after 24 hours of serum	Blood invasion		Outcome. Day of beginning recovery or death
			In 1st 24 hours	Total within 48 hours	Before immune serum	24 hours after beginning of immune serum		Before serum	After serum	
1. (J. T. A.).....	I	2d	300 cc.	600 cc.	0	1 : 640	+	0	0	R. 4th day
2. (G. B.).....	I	5th	40,000 u.	same	10^{-5}*	10^{-3}*	0	0	0	R. 6th day
3. (M. E.).....	I	6th	60,000 u.	same	0	1 : 320	0	0	0	R. 6th day
4. (G. F.).....	II	2d	80,000 u.	100,000 u.	0	1 : 320	0	0	−	R. 4th day
5. (G. G.).....	I	7th	100,000 u.	same	0	1 : 2560	0	+	0	R. 7th day
6. (G. H.).....	I	3d	80,000 u.	same	0	1 : 2560	0	0	−	R. 4th day
7. (R. H.).....	I	3d	110,000 u.	130,000 u.	0	1 : 1280	0	0	−	R. 5th day
8. (J. L.).....	I	4th	300 cc.	900 cc.	0	1 : 320	0	0	0	R. 7th day
9. (E. M.).....	I	1st	80,000 u.	same	0	1 : 5120	0	+	0	R. 2d day
10. (A. M.).....	I	3d	300 cc.	550 cc.	0	1 : 640	0	+	0	R. 6th day
11. (A. M.).....	II	1st	80,000 u.	177,000 u.	0	1 : 320	0	0	0	R. 6th day
12. (W. H. Mc).....	I	7th	300 cc.	same	0	1 : 1280	0	0	0	R. 8th day
13. (I. B. M.).....	I	4th	60,000 u.	120,000 u.	0	1 : 1280	0	+	0	R. 6th day
14. (R. O.).....	I	1st	100 cc. 15,000 u.	100 cc. 70,000 u.	0	1 : 40 (After only 50 cc. ser.)	+	0	0	R. 4th day
15. (A. S.).....	I	5th	80,000 u.	120,000 u.	0	1 : 2560	0	0	0	R. 7th day
16. (F. S.).....	II	1st	80,000 u.	same	0	1 : 1280	0	0	0	R. 2d day
17. (M. T.).....	I	3d	50,000 u.	70,000 u.	0	1 : 80	0	0	0	R. 5th day
18. (T. W.).....	I	3d	70,000 u.	150,000 u.	0	1 : 320	0	+	0	R. 7th day
19. (E. Z.).....	I	5th	300 cc.	600 cc.	0	1 : 1280	?	+	0 (Later = +)	D. 12th day

TABLE I (*continued*)

Case number	Type	Day of disease immune serum treatment begun	Amount of immune serum injected†		Titer of pneumococcidal-promoting activity of patient's serum		Spread of lesion after 24 hours of serum	Blood invasion		Outcome. Day of beginning recovery or death
			In 1st 24 hours	Total within 48 hours	Before immune serum	24 hours after beginning of immune serum		Before serum	After serum	
20. (F. P. R.).....	I	4th	300 cc.	700 cc.	0**	1 : 640	0	0	—	R. 7th day
21. (K. R. R.).....	I	5th	150 cc.	730 cc.	0	1 : 320	—	—	—	R. 12th day
22. (H. Y. T.).....	I	5th	300 cc.	500 cc.	0	1 : 320	0	0	—	R. 6th day
23. (H. S.).....	I	4th	300 cc.	900 cc.	0	1 : 80	?	+	0	R. 9th day
24. (B. M.).....	I	3d	300 cc.	500 cc.	0	1 : 320	0	0	—	R. 4th day
25. (L. W. P.).....	I	11th	300 cc.	same	1 : 10	1 : 640	0	0	—	R. 11th day
26. (F. M. Y.).....	I	5th	250 cc.	same	0	1 : 1280	0	0	—	R. 6th day
27. (L. Y.).....	I	12th	200 cc.	same	0	1 : 160	0	0	—	R. 12th day
28. (L. K. Y.).....	I	6th	300 cc.	400 cc.	0	1 : 80	0	0	—	R. 8th day
29. (W. F.).....	I	2d	400 cc.	same	0	1 : 1280	0	0	—	R. 2d day

† In column under heading "Amount of immune serum injected" the unconcentrated serum is designated in cc. while the concentrated antibody solution (Felton) is indicated in units.

The figures in the column under "Titer of pneumococcidal-promoting activity of patient's serum" indicate that dilution of the patient's serum which when added to 0.2 cc. of fresh rabbit serum + rabbit leukocytes (concentration of W. B. C. as before) is capable of destroying 10^{-6} of the standard suspension of pneumococci.

* In this case pneumococcidal tests were made only on the whole serum. The increase in the number of organisms killed, from 10^{-5} (of the standard suspension) before serum to 10^{-3} afterwards indicates a decided increase in the pneumococcidal-promoting power of the serum.

** Two days earlier the serum of this patient had shown a pneumococcidal-promoting titer of 1 : 20 as well as mouse protection action.

TABLE II

Relation of pneumococcidal-promoting titer of patient's serum to length of disease course in cases treated within the first three days

Case number and type	At beginning of serum treatment		Day of disease on which immune serum begun	Day of recovery	Titer of pneumococcidal-promoting activity of patient's serum in days following the first 24 hours of serum treatment*					
	Extent of lung area involved **	Bacteremia			1	2	3	4	5	6
11. (A. M.) II.....	L1/4	0	1st	6th	1 : 320	—	1 : 160	1 : 320	1 : 40	
14. (R. O.) I.....	L1/3	0	1st	4th	1 : 40	1 : 2560	1 : 640			
16. (F. S.) II.....	R1/4	0	1st	2d	1 : 1280					
9. (E. M.) I.....	R1/2	+	1st	2d	1 : 5120					
1. (J. T. A.) I.....	L1/8	0	2d	4th	1 : 640	1 : 320				
4. (G. F.) II.....	R1/6	0	2d	4th	1 : 320	1 : 320				
29. (W. F.) I.....	R1/2+L1/2	0	2d	2d	1 : 1280					
6. (G. H.) I.....	R1/8	0	3d	4th	1 : 2560					
7. (R. H.).....	R1/8	0	3d	5th	1 : 1280	1 : 2560				
10. (A. M.) I.....	L1/3	+	3d	6th	1 : 640	1 : 2560	1 : 5120			
17. (M. T.) I.....	L1/4	0	3d	5th	1 : 80	1 : 40				
18. (T. W.) I.....	L1/3	+	3d	7th	1 : 320	1 : 320	1 : 160	1 : 160		
13. (I. B. M.) I.....	L2/3	+	3d	4th	1 : 320					

* The daily serum titer up to and including the day of beginning recovery is recorded.

** The figures L1/4, R1/2, etc. indicate the approximate area of the left and right lung fields occupied by the x-ray shadow.

adjacent lobe in the presence of well marked pneumococcidal-promoting activity of the serum. Extension of the process occurred for one day only when the disease was cut short by crisis on the 4th day. The other case, Number 14 (R. O.), required desensitization and obtained considerably less than the usual amount of serum in the first twenty-four hours. In two additional patients there was a questionable spread of the lesion after the first day's treatment. The x-rays showed increasing density of already involved areas which might well be interpreted as indicating more effective localization of the disease process. Thus, while it is not possible to make any comparison with untreated cases on a statistical basis, it does seem that in this series of patients, spread of the disease occurred less often than is observed in cases of Types I and II lobar pneumonia that are not treated with serum.

Effect of immune serum on bacteremia

Positive blood cultures were obtained in six cases before the beginning of serum treatment. The highest colony count was 9 per cc. of blood. In every case the cultures became negative within twenty-four hours and remained so with one exception. This patient, Number 19 (E. Z.), an old woman 77 years of age, had apparently recovered from her disease when, after four days without fever, she rapidly became comatose and died. On the day of death, the blood was found to contain pneumococci and to be without pneumococcidal-promoting properties. Thus, there would appear to be a direct relationship between the presence of an excess of circulating pneumococcal immune substances and the localization of pneumococci in the lung lesion. However, in none of our cases were there more than a few colonies of pneumococci found in blood culture, a fact which necessitates caution in drawing inferences from this study.

The relation of treatment by immune serum to the length of the course of the disease

The duration of the disease in the serum treated cases was found to depend largely on the time at which the serum was begun (Tables I and II). Six of the seven patients treated in the first forty-eight hours of the disease recovered within four days [2] (Table II). In the seventh case, caused by pneumococcus Type II, the disease continued until the sixth day, although treatment was begun on the first day of his illness. Of three Type I cases treated within 30 hours of onset two (Cases 9 and 29) recovered promptly. The third (Case 24) receiving an inadequate amount of serum because of sensitivity to horse protein did not recover until the 4th day. One of the two Type II patients treated in the first 24 hours showed an

[2] The day on which the final decline in temperature, pulse and respiration began is taken as the day of recovery.

immediate response. The other was the case just mentioned. Of six patients treated for the first time on the third day of the disease, four recovered within five days, the other two on the 6th and 7th days respectively. When immune serum was given after the third day, it appeared to have little effect on the duration of the disease (Table I) and Chart I and II.

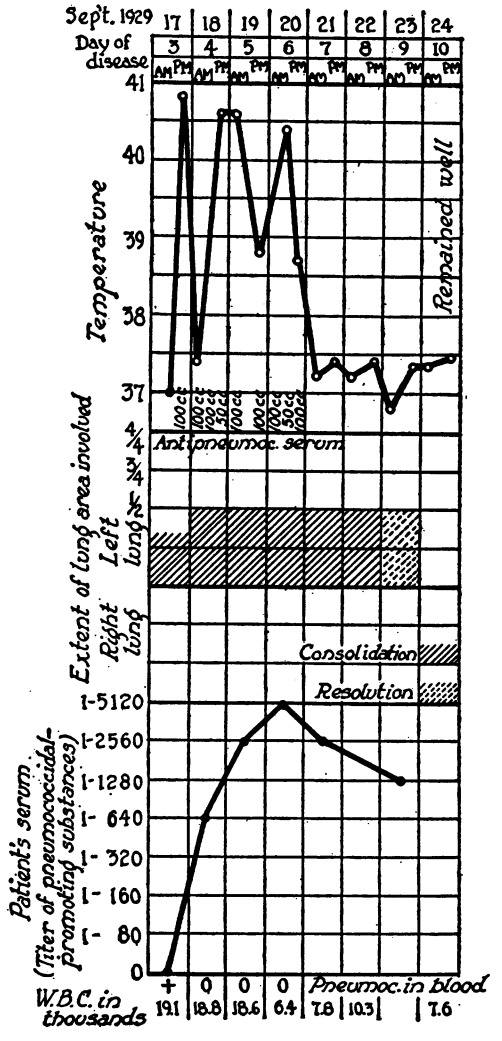

CHART I. CASE 10 (A. M.). LOBAR PNEUMONIA. PNEUMOCOCCUS TYPE I ISOLATED FROM THE LUNG

The relationship of the titer of the pneumococcidal-promoting activity of the serum to the continuance of the disease is difficult to evaluate from the data given in Table II. In certain cases the disease persisted from three

to five days in the presence of a concentration of circulating immune substances as high or higher than that shown by other cases in which recovery occurred within twenty-four to forty-eight hours after the first dose of

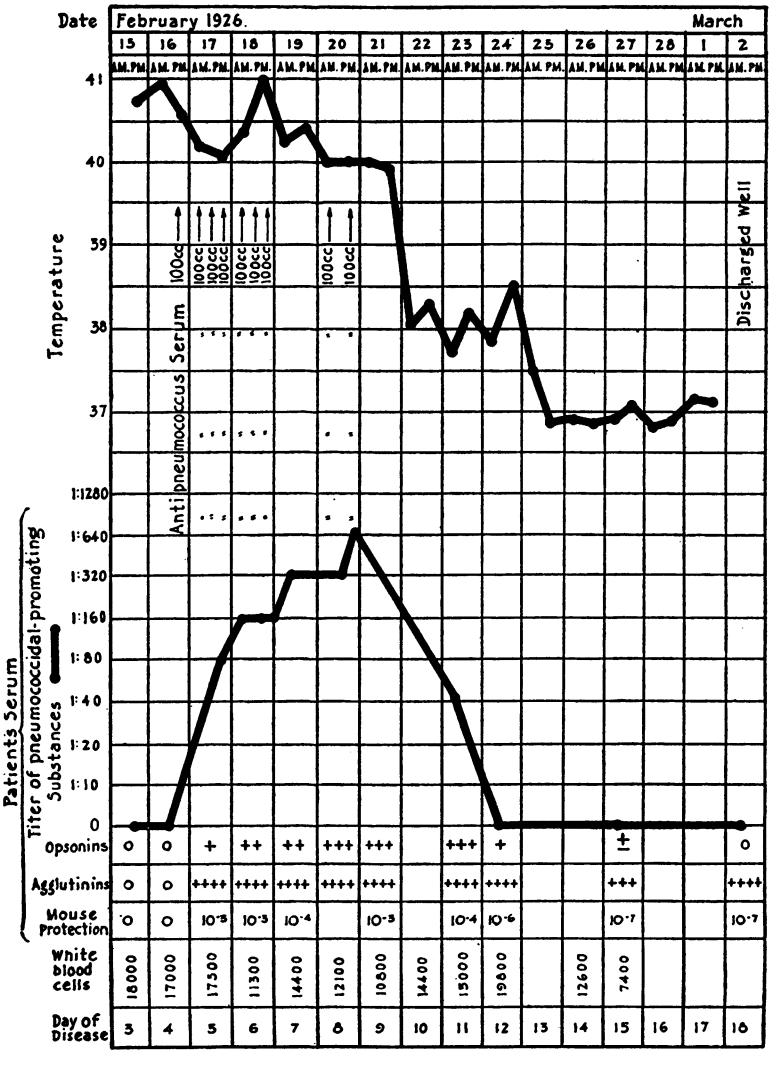

CHART II. CASE 23 (H. S.). LOBAR PNEUMONIA. PNEUMOCOCCUS TYPE I ISOLATED FROM THE BLOOD. SERUM TREATMENT BEGUN ON THE 4TH DAY OF THE DISEASE.

serum. It is true that the highest initial titers of serum activity were found in those patients recovering within twenty-four hours after the beginning of treatment, but that only moderate concentrations of immune bodies may bring about the same effect was shown by Case 13 (I. B. M.), Table II.

There was no observed relationship between the extent of pulmonary involvement present at the time serum was begun and the duration of the

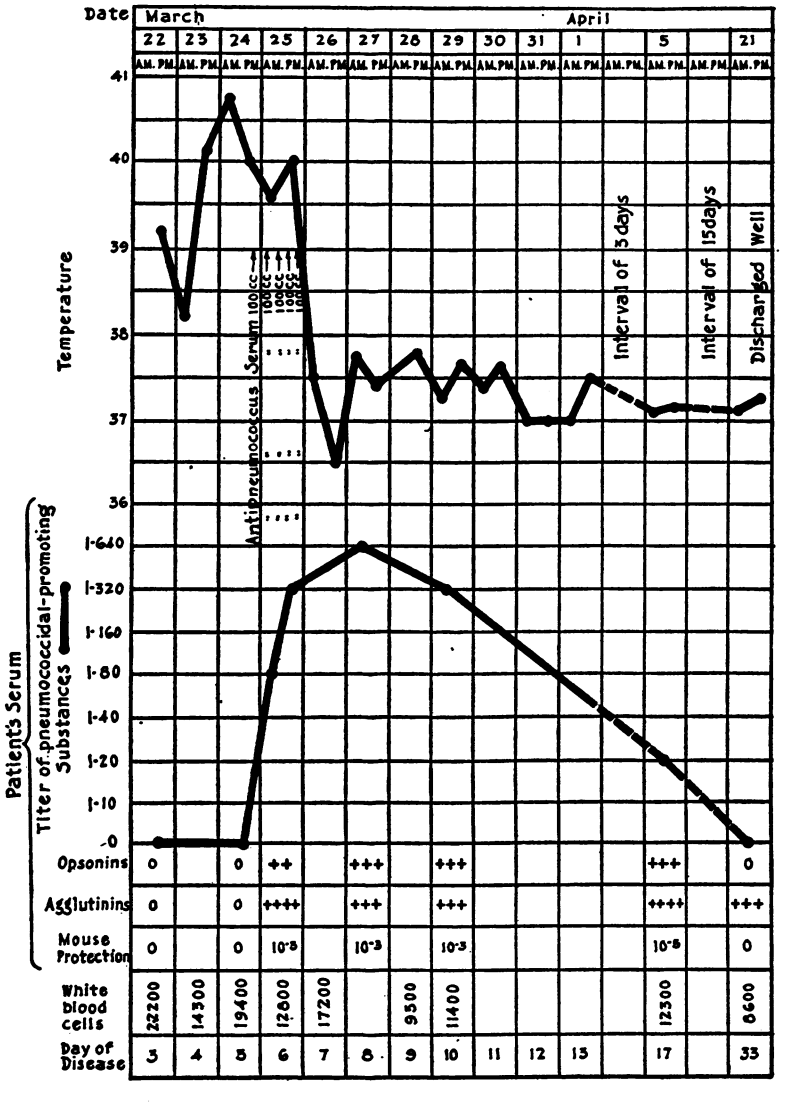

CHART III. CASE 22 (H. Y. T.). LOBAR PNEUMONIA. PNEUMOCOCCUS TYPE I ISOLATED FROM THE SPUTUM. SERUM TREATMENT BEGUN ON THE 5TH DAY OF THE DISEASE.

disease thereafter. In fact, the two patients, Cases 29 and 13, showing the most extensive lesions, recovered within twenty-four hours after the initiation of immune serum therapy.

Effect on resolution

The injection of immune serum appeared to have no effect on hastening the onset of resolution except in two cases in which treatment was begun on the first day of the disease. These two patients, Cases 9 and 16 (Tables I and II) both had a crisis the day following the initiation of treatment. One showed definite signs of beginning resolution on the 3d day after the onset of the disease and the other on the 4th day. A third case, Number 11, Pneumococcus Type II, treated on the first day of his illness, did not recover until the 6th day when resolution was first noted. Patients treated on the second day or later showed resolution occurring from the 6th to the 9th days after onset, even though the course of the disease was shorter than usual.

Comparative observations in the several manifestations of humoral immunity in the patient's serum

In certain cases, tests for the opsonic, agglutinative and mouse protective, as well as the pneumococcidal-promoting activity, were made on the same sample of serum. The results of such observations are illustrated in Charts II and III. Before the injections of immune serum and for some days afterwards, there was found to be a close parallelism between these different reactions. However, with the diminution of pneumococcidal-promoting potency of the patient's serum, there occurred in most of the cases tested, a curious disparity between the agglutinating properties of the serum and its other antipneumococcal manifestations. As will be noted in the accompanying charts, final tests showed little or no pneumococcidal-promoting, mouse protective or opsonic activity, but a marked and practically undiminished agglutination reaction. We made no further studies as to the nature of this phenomenon and have no explanation to offer.

Mouse protective action was found to be a somewhat more delicate test for antipneumococcal properties of the serum than was its pneumococcidal-promoting action as tested here. However, the latter is considerably more sensitive to quantitative estimation and gives more regular results.

DISCUSSION

The majority of reports on the use of antipneumococcus serum in the treatment of lobar pneumonia have dealt principally with its effect on mortality. A few studies have included observations on those objective changes occurring during the course of the disease which may be attributed to the introduction of the immune serum. The inhibiting action of antipneumococcus serum on the spread of the pneumonic lesion, first reported by Cole (3) in Type I pneumonia has been confirmed by later workers. Finland and Sutliff (4) found likewise that in Type II pneumococcus pneumonias treated with large doses of Felton's concentrated antibody

solution, extension of the lesion ceased in every case. The data for these observations were secured both from physical examinations and x-ray, although details as to the frequency of x-ray examinations, the extent and location of the shadow, etc., are not given. Our observations which are based on daily x-ray examinations agree substantially with those of the afore mentioned workers. The one exception among 29 cases, that of a spread to a new lobe occurring in an early well treated patient subsequent to the first twenty-four hours of therapy, represents the occasional failure of even a high concentration of circulating antipneumococcus immune bodies to check the extension of the lesion. However, growth of the pathological process ceased within forty-eight hours and the patient recovered on the fourth day of the disease.

Another and even more significant effect of antipneumococcus serum which has been found to occur constantly, is its power to control bacteremia. In Cole's report (5), of 431 cases of Type I lobar pneumonia treated with serum, among which 140 showed blood invasion before the initiation of specific therapy, the blood became sterile in all but three instances. These three patients showed initial colony counts of several hundred pneumococci per cc. of blood. Even in cases with intense bacteremia the injection of immune serum in large doses was found to produce a marked reduction in the number of micro-organisms in the blood or at times, their complete disappearance. Sutliff and Finland (4) (6), and Cecil and Plummer (7), report analogous results in both Types I and II lobar pneumonia treated with concentrated antibody solution (Felton).

As to whether the course of the disease is shortened by the administration of immune serum, there is less unanimity of opinion. Locke (8) found no difference between serum treated and control patients in the duration of the disease, although he notes that in patients treated within the first three or four days of the disease the subsequent temperature curve was lower than in the untreated cases. On the other hand, Cecil and Sutliff (2) found in a larger series of cases, including both Types I and II lobar pneumonia, that the mean temperature curve of the serum treated cases was about two days shorter than that of the control untreated patients. Likewise, Armstrong and Johnson (9) observed that the course of the disease in the cases treated by Type I antiserum was shortened two and one-half days and the cases treated by Type II antiserum one and one-half days as compared with an equal number of controls. Sutliff and Finland (6) and Finland and Sutliff (4) found that in cases treated on or before the fourth day, recovery occurred one to two days earlier than in the untreated patients. Our observations coincide with those of the last named authors although in individual cases there was no evidence that the disease was abbreviated when treatment was initiated later than seventy-two hours after onset. The most striking effect of serum is seen in Type I patients treated

within the first twenty-four hours of the disease. Recovery usually occurs promptly.

Granted that the duration of the disease is in general shortened by the administration of immune serum and the evidence available supports this inference, there still remains a number of instances in which the disease persists actively for days despite a high concentration of injected specific immune substances in the blood. This condition which we have observed repeatedly presents a problem of great interest in relation to the mechanism of the action of immune serum. The data obtained on such cases fail to reveal any unusual bodily state which might interfere with the full action of serum. Case 10 (A. M.) Chart I for example, showed an x-ray shadow covering only one-third of his left lower lung field and a bacteremia of 1 colony per cc. of blood at the time of beginning serum treatment on the 3d day of the disease. After twenty-four hours of serum treatment (300 cc.) the blood culture was sterile, and the process, which now occupied only half the lung field, stopped spreading. The concentration of immune substances in his blood increased to a point considerably beyond that shown by the average patient recovering spontaneously, but the symptoms and signs of the disease persisted until the night of the 6th day. In this patient the number of white blood cells was rather low during the last two days of his illness, but a well marked leukocytosis was present before that time. This patient in a second attack of lobar pneumonia, due to pneumococcus Type II (Case 11) showed the same phenomenon of a prolonged disease even though antibody solution was begun on the first day of the disease and a fair concentration of immune substances was maintained during the six days of his illness. The leukocytes did not rise above a high normal at any time. It is very doubtful, however, whether the lack of a high white count had anything to do with the prolonged course of the disease, since patients exhibiting this same condition often have had marked leukocytosis.[3]

Another patient (Case 20, Table I and Chart II) grew steadily worse symptomatically during the first three days of intensive treatment, becoming comatose on the 7th day of the disease. While the serum checked

[3] In a previous study of the pneumococcidal action of mixtures of rabbit serum and leukocytes containing specific antipneumococcus serum, it was found that the presence of a small amount of fresh normal serum was essential to the reaction. This activating effect of the normal serum could be abolished by heating it at 56° C. for one-half hour or by ageing the serum. In order to determine whether this property of the normal serum is diminished during pneumococcus infection, pneumococcidal tests were made in which serum secured from pneumonia patients at various stages in the disease was substituted for normal rabbit serum. It was found that the activating effect of the serum in lobar pneumonia was not impaired to any appreciable degree (22). Hence, the apparent failure of the immune serum to exert its expected action in the cases described above is not to be attributed to such a deficiency of the circulating blood fluid. The state of the functional activity of the leukocytes in lobar pneumonia has been discussed in the preceding paper.

blood invasion and the lesion remained confined to the two lower and right upper lobes, no antitoxin action could be ascribed to the immune serum. The possible implications of these observations will be discussed at the end of the paper in connection with the general significance of immune bodies.

Wadsworth (10) has summarized the reports on 853 cases of Type I pneumonia treated with whole antipneumococcus serum which showed a mortality for the group of 12.4 per cent. Including an additional 200 cases reported by Cole (5) which were not included in Wadsworth's group, the mortality on more than 1,000 serum treated cases would not be over 12 per cent. Cole's figures on 431 cases treated at the Hospital of the Rockefeller Institute gave a mortality of 10.2 per cent. Most reports on the results of treatment of Type I pneumonia with concentrated antibody solution (Felton) have shown a considerably higher mortality. Cecil and Plummer's (11) series of 239 cases showed a mortality of 20.1 per cent. Park, Bullowa and Rosenblüth (12) report a death rate of 17 per cent in a series of 109 cases. In each of these two series the control cases showed a higher mortality than that given by Wadsworth, the result being that the relative reduction of mortality in patients treated by these two kinds of immune serum is not very different. However, a somewhat more favorable report on the use of Felton's antibody solution has been recently made by Heffron and Anderson (21) who observed a mortality of only 10.6 per cent among 188 Type I cases treated within the first four days of the disease, as compared with 25.9 per cent mortality on the control series. Results of treatment of pneumococcus Type II pneumonia with antibody solution have been for the most part less favorable. In Cecil and Plummer's (7) series of 252 serum treated cases, there was a mortality of 40.5 per cent as compared with 45 per cent in the control cases. Park and his co-workers (12) reported 56 cases with a mortality of 23 per cent as opposed to 30 per cent in the untreated cases. On the other hand Finland and Sutliff (4) treated a series of 46 cases with a mortality of 20 per cent as contrasted with a mortality of 40 per cent in 81 untreated cases. These latter authors used considerably larger doses of antibody solution than had been previously employed. These results obtained by a number of workers show without any doubt that the administration of antipneumococcus immune serum of high potency in adequate dosage brings about reduction in mortality in Type I pneumococcus lobar pneumonia and to a less, but definite degree in pneumonia caused by Type II. When the serum is administered within the first three days of the disease the death rate is further diminished. In several large series the mortality per cent of patients treated in the first 72 hours of the disease is half that of the group mortality.

It has been found by all observers that patients showing an initial bacteremia respond much less well to the serum. The presence of blood invasion as Bloomfield (13) pointed out indicates that the body's defense mechanism has already begun to break down and hence the therapeutic

serum which, as we know, depends for its action on the co-operation of the tissues, could not be expected to exert its maximum beneficial effect in such cases. It is of much interest to inquire in this connection into the cause of death of serum treated patients in whom the blood has become sterile under the influence of serum and the spread of the lesion arrested. An analysis of the fatal cases such as is given by Cole (5), Cecil and Plummer (11), Finland and Sutliff (4) shows that the majority of patients dying after treatment with immune serum have some severe complicating condition either present before or developing during the pneumonic process. A certain small percentage of patients, however, in whom treatment was begun moderately early in the course of the disease and continued adequately, have gone on to a fatal termination without complications and with a well localized and relatively circumscribed pulmonary infection.

In attempting to elucidate this problem, it would be important to know how frequently death occurs in patients who were not treated by serum and who showed involvement of single lobes with sterile blood cultures and no complications. Unfortunately, little has been written on the subject. However, two valuable studies on Types I and II pneumonia (as yet unpublished) have recently been made by Sutliff and Finland [4] which include pertinent data. Sutliff found that of 19 Type I pneumonia patients dying with only a single lobe consolidated, six showed sterile blood cultures during life and three of them died without complications. Finland had a series of 24 fatal Type II cases with the pneumonic process confined to one lobe, five of which died without detectable bacteremia. His data did not include the presence of complications. Both these investigators have made similar observations on smaller groups of patients treated by serum. Of Sutliff's nine cases dying with a single lobe involved, seven showed negative blood cultures and five of them had no complications. It is true that in this series certain cases received small amounts of serum and others were in the very old age group, but the significant fact is that they died with a well localized lesion of one lobe only. In Finland's series, of six serum treated cases dying with the lesion confined to a single lobe, three showed an absence of bacteremia.

How then are all these various observations on the use of immune serum to be explained and coordinated? Why is it that the injection of an adequate dose of antipneumococcus serum within the first 24 to 30 hours of the infection commonly brings about prompt recovery, while beginning the treatment later in the disease results at best in shortening its course by a day or so, or if serum is started after the third day, in the persistence of the process until time of usual spontaneous recovery? How are we to account for the striking action of the immune serum in checking bacteremia and limiting the spread of the lesion, in relation to its apparent inability in

[4] We are greatly indebted to Drs. Sutliff and Finland for their courtesy in sending us this material and permitting us to use it.

many instances to bring about a cessation of the activity of the disease process before the period of its natural termination? And why do some patients die with only a single lobe involved and no blood invasion? While unequivocal answers to these questions are not possible without much more data than is at present available, we would like to propose a viewpoint based on inferences derived from our work and that of others.

It is well known that mixtures of fresh normal leukocytes and highly potent antipneumococcus serum with a small added quantity of fresh normal serum are capable of exerting marked pneumococcidal action under conditions providing maximum contact between the pneumococci and the leukocytes. The early developing intra-alveolar exudate in lobar pneumonia consists of edema fluid into which pour an increasing concentration of young active polymorphonuclear leukocytes (14). By means of the respiratory movements and the increasing accumulation of fluid and cells within the alveoli, the suspended pneumococci are brought into intimate contact with the cellular elements. While the natural antibodies are active and produce a certain degree of opsonization, as we were able to observe in experimental lobar pneumonia in the dog and early lesions in human beings (15), they are not present in sufficient concentration to check the expansion of the lesion. If, however, at this stage, a high concentration of immune substances is produced in the blood stream, the process of phagocytosis and intracellular digestion is so enhanced as to bring about a rapid diminution in the number of invading micro-organisms and the consequent termination of the infection. As the lesion progresses, the alveoli become packed with leukocytes, fibrin is laid down, the whole mass of diseased tissue becomes less mobile and there is a decrease in the richness of the blood supply. In our study of the x-ray changes in lobar pneumonia (16), we found that it usually required about three days for the lesion to reach its maximum density. It is after this stage that the introduction of immune serum is less effective. Various ideas have been put forward in an attempt to explain the phenomenon, chief among which is the lack of penetration of the immune substances into the diseased area because of obstructed blood supply. The objection to this conception is the lack of evidence of a markedly defective circulation in the well consolidated lesion. If a serious impairment of the blood supply was present, one would expect much more necrosis of the lung tissue than is found in the uncomplicated lesion at autopsy. Furthermore, the toxic manifestations of the disease indicate the constant liberation of injurious substances from the infected area and the presence of circulating specific soluble substance gives evidence that large molecular structures can pass through into the blood stream. It seems to us more likely that the leukocytes of the intra-alveolar exudate gradually lose their functional activity and hence are unable to cooperate with the immune substances after a certain period of time. The active life of the polymorphonuclear leukocyte has been variously estimated from two or three to four

or five days so that unless there is a constant accession of new cells [5] the exudate would contain more and more dead and dying leukocytes as the disease progresses. Studies by Kredel and Van Sant (17) on the exudate of the lesions in experimental lobar pneumonia in dogs show that the relative number of dead leukocytes increases progressively after 24 to 48 hours. We have some evidence from both perfusion experiments on the lungs of experimental pneumonia as well as on the studies of tissues that the dog maintains a more abundant blood supply in the consolidated lung and shows much less intra-alveolar fibrin than does the human being, hence we should except an even greater proportion of inactive leukocytes in human pneumonic lung. The increasing immobility of the progressively consolidating lesion may also interfere with the optimum action of the serum and leukocytes, and no doubt, diminished blood supply, such as is apparently present in the stage of gray hepatization, plays a rôle. If this is the correct interpretation of the effect of immune serum, the action of a high concentration of circulating immune substances in preventing a spread of the lesion is readily understandable since any new implantation of pneumococci presents the same favorable conditions for the action of the antipneumococcal immune bodies and leukocytes as does the initial lesion.

What action, if any, can be ascribed to immune serum in bringing about recovery when administered after the lesion has been well established? Our observations on the occurrence of acquired immune substances presented in Part II of this study provided no evidence that recovery was dependent on or even necessarily associated with the presence of circulating immune bodies. Further evidence of the same nature is afforded by the numerous instances of serum-treated patients in our series showing a very high concentration of immune substances for many days preceding recovery. It is true that such patients all recovered, but the initiation of the recovery process cannot be ascribed to the antipneumococcal activity of the serum, except insofar as it inhibited bacteremia and prevented spread of the lesion. Are these two effects of the immune serum sufficient to account for the lowered mortality of patients treated after the early stage of the disease? While adequate data for a statistical solution of this question is not available, certain facts relating extent of pulmonary involvement and bacteremia to outcome are well recognized. It has been long known that with spread of the pneumonic lesion from lobe to lobe the mortality rises rapidly. In a study of 658 autopsies on lobar pneumonia patients made by Chatard and summarized by Cole (19) 17 per cent of them showed only a single lobe consolidated whereas the two lobe involvements comprised 34 per cent of the total. Again the prognostic significance of bacteremia has been pointed out repeatedly in recent years. In a series of 149 cases of

[5] Loeschke (14) considers that there is a re-accumulation of leukocytes in the consolidated area, but Lauche (18) and others find no evidence for this. Our observations would lead us to concur with these latter workers.

Type I, II and III pneumonia studied by Rosenblüth (20), the mortality of patients with bacteremia was 80 per cent, but only 18 per cent in those without blood invasion. Similarly Cecil and Plummer (7) report a mortality of 87 per cent of Type II cases with bacteremia and 8 per cent without bacteremia. Thus, taking these facts together, it seems obvious that limiting the extent of the infection in the lung and preventing the escape of pneumococci into the blood stream would result in a considerable reduction in mortality. It is also possible that the same action of the immune bodies on the pneumococci in the lesion which is so marked in the early stage, goes on at a slower rate in the older process. Again there may be other effects of the immune serum. Cole, Cecil and others have observed a slight but definite lowering of the fever following the administration of serum in adequate dosage which suggests some antitoxic action. If such an effect is exerted it might account for the briefer course of the disease in serum treated patients reported by certain investigators, in that under condition of lessened toxicity the body is enabled to develop its natural mechanism of recovery more rapidly than otherwise. That the antitoxic effect of immune serum plays more than a minor rôle in the therapeutic action seems unlikely in view of those cases studied by Sutliff and Finland which died with only a single lobe involved, a sterile blood and no complications. However, it should be pointed out here that in Cole's larger series of cases, there were no deaths among patients showing analogous conditions of the disease.[6] This may be significant in relation to the therapeutic preparation employed. Cole used whole antipneumococcus serum, while both Sutliff and Finland used concentrated antibody solution. In our study we were unable to detect any difference between the effects of the two preparations.

SUMMARY

A study of twenty-nine cases of pneumococcus lobar pneumonia treated with specific immune serum was made with the purpose of determining the effect of serum therapy on the spread of the pneumonic lesion, bacteremia, the length of the disease and resolution of the consolidated lung. In twenty-six of the patients the disease was due to Pneumococcus Type I, the remaining three to Pneumococcus Type II. Two preparations of immune serum were used; whole serum Type I, with which the majority of the cases were treated and concentrated antibody solution (Felton) Types I and II. The concentration of antipneumococcal immune substances in the patients' serum was determined by testing its pneumococcidal-promoting power. X-rays of the chest were made daily throughout the course of the illness.

Following the first twenty-four hours of serum treatment, extension of

[6] Dr. Rufus Cole in a personal communication has kindly supplied me with this data supplementing his analysis of fatal serum treated cases to which reference has been made (5).

the pulmonary lesion ceased in all but two instances. One of these received an inadequate amount of serum in the first twenty-four hours because of necessary desensitization. The other, adequately treated, showed nevertheless, a spread of the process to a new lobe, but recovered on the fourth day of the disease. Bacteremia terminated in every case with the institution of specific therapy. The effect of immune serum on the course of the disease was found to depend largely on the stage of the illness at which treatment was begun. In the majority of cases treated within the first three days after onset, the course of the illness was shortened by a day or two. Six of the seven patients treated in the first forty-eight hours of the disease recovered within four days. Five of these patients received the first dose of serum within thirty hours of the onset; three of them recovered promptly, and two showed signs of beginning resolution on the third and fourth days respectively after the inception of the disease. In no other instances was there any evidence that serum treatment hastened resolution. When serum was begun after the first three days, the disease usually continued actively until the time of its natural termination despite the presence frequently of a very high concentration of antipneumococcal immune substances in the blood. This finding is of especial interest in relation to the mode of action of immune serum in pneumonia. Our observations and those of others suggest that in the early phases of the disease before consolidation has developed to its maximum intensity, the specific antibodies are capable of so affecting the pneumococci in the lesion as to bring about a rapid cessation of the disease process. But after this stage has been reached the chief effect of the injected immune substances is to confine the pneumococci to the pulmonary lesion and to prevent extension of the pathological process, the actual termination of the disease being occasioned by the unknown process of natural recovery. Data in support of these inferences and evidence that immune serum exerts a favorable influence on outcome even when administered after the disease has developed fully, are presented in detail.

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