TWENTY-THREE CASES OF PNEUMONIA TREATED WITH ANTIPNEUMOCOCCUS SERUM *

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Through the cooperation of the Research Laboratory I was able to give a series of patients suffering from lobar pneumonia an antipneumococcus serum, and although the results were somewhat inconclusive, it seems desirable to publish them.

The series includes practically all of the pneumonia patients admitted to the service of the Second Medical Division of New York Hospital during the period of the test. This division receives all medical patients admitted to the hospital on the even days of the month, while those admitted on the odd days go to the first division. Although this method of assignment does not give a strict alternation of patients, yet it seemed justifiable to use the patients on the first division as controls, inasmuch as none of them received any serum.

The serum was taken from a horse immunized against many strains of pneumococci.¹ Usually it was injected directly into a vein of the arm at a temperature about that of the patient. This rule was departed from and the serum was given subcutaneously to two children on account of the difficulty of entering the vein with the needle, and also when second and later doses were given to four adult patients who had received the initial dose intravenously. The first doses for adults in the earlier cases was 100 c.c. This was increased later until, in one instance, an initial dose of 300 c.c. was given. Many of the patients received more than one dose so that the total amount of serum that an individual received ranged from 50 to 750 c.c. This maximal quantity was given in six doses spread over a period of five days.

A complete demonstration of the nature of the infecting organism was not essayed. Blood-cultures, however, were made in eleven cases. Only one of them (Case 11) showed the pneumococcus, the others being negative. In Case 6, pneumococci were cultivated from pus from the pleural cavity. Cultures were made from the sputum in several instances.¹ The diagnosis was based on the clinical evidences of pneumonia, special weight being given to the presence of rusty sputum and

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* From the New York Hospital and Research Laboratory, Department of Health, City of New York.

1. See Notes on Serum, Cultures, Etc., following.

the physical signs of a definite consolidation of the lung. In every case the subsequent course of the illness confirmed the diagnosis of lobar pneumonia and strengthened the probability of the existence of a pneumococcus infection.

The chief points of note in these cases are given in a very condensed form in Table 1, together with the details of the dosage of the serum. The time of onset of pneumonia is not uncommonly indefinite. Many patients give a history of an indefinite illness lasting for several days, during which time they may not have been confined to bed continuously. This may explain the duration of some of the more protracted cases of this series. Most of the patients, however, gave symptoms that fixed the beginning of the pneumonia with a reasonable degree of accuracy.

A review of the data of Table 1 shows that the series included twenty-three cases with sixteen recoveries and seven deaths, a mortality of 30.5 per cent. Of the seven patients who died, three were alcoholics, one of whom had suffered from two previous attacks of pneumonia, and all were very actively delirious. A fourth death was that of a baby (Case 4), who, in addition to pneumonia, had multiple abscesses of the scalp, double purulent otitis media, and empyema followed by pneumothorax. The remaining three deaths seemed to have been due to the frank intensity of the pneumonia.

Of the sixteen patients who recovered, eight had defervescence by crisis and eight by lysis. The crisis occurred on the following days: fourth, fifth to sixth, sixth, seventh, ninth, eleventh, twelfth, and on the eighteenth to nineteenth. The onset of the lysis in the other cases in which the patients recovered occurred on the following days: sixth, seventh (three cases), eighth, tenth and on the thirteenth day. In the remaining cases the onset of the lysis was scarcely definable because the fall of temperature was so gradual. Five patients had complications. In one instance this was serous pleurisy (Case 5). In cases 6 and 19 empyema developed. In Case 4 the signs and symptoms were those of empyema, but an exploratory puncture failed to find the pus. On the next day, however, there was evidence of pneumothorax, and on operation considerable pus was found. Two days later the child died with edema of the lungs. She was extremely ill from the time of admission and had in addition to the pleural complications, double otitis media for which the drum membranes were incised, and also many abscesses of the scalp. Otitis was detected in Case 18 also. The series offered an opportunity to observe the effects of the administration of large and frequent doses of horse-serum that had not been refined in any manner and that contained no preservative except a trace of chloroform.¹ Usually no immediate effects could be detected and the injection of the serum was

TABLE 1.—SUMMARY—

Case No.	Sex,* Age in Years, Habits, Etc.	Condition of Patient				Blood-Culture, Etc.
		Day of Admission	Invasion	Temperature Pulse Respiration	Site Lesion	
1	♂ 12	3	Chill	T. 104°-5° P. 132 R. 28	L. L.	Sterile
2	♀ 1¼	15 (?)	Chill	T. 104.8° P. 160 R. 50	R. U. L. U.	
3	♂ 41 Alcoholic	8	Chill	T. 103° P. 124 R. 48	R. M. R. L.	
4	♀ 5	6		T. 106° P. 140 R. 48	R. U.	
5	♂ 26	2	Chill	T. 106° P. 116 R. 28	L. L.	Sterile
6	♂ 17	4	Chill	T. 105° P. 128 R. 40	R. L.	Sterile
7	♂ 30	5	Chilly	T. 103.6° P. 108 R. 32	R. U. R. M.	
8	♂ 30	2	Chill	T. 105° P. 112 R. 24	R. U.	Sterile
9	♀ 29	2	Cough, pain	T. 103° P. 140 R. 40	R. L.	Sterile
10	♂ 46	7	Chill	T. 104.6° P. 108 R. 32	L. L.	Sterile

* In this column ♂ denotes male and ♀ female.

Serum Administration			Outcome of Disease			
Day of Disease	Dose, Methods	Effect	Termination of Case	Serum Sickness and Day of Disease it Appeared	Complications	Remarks
4	50 c.c. intrav.	Chill. T. 3°+	Crisis 4th day. Recovery.	Purpuric rash, arthritis 8th day.		Crisis a few hours after serum.
15	30 sube.		Crisis 18th and 19th days. Recovery.			First and second injections without effect.
16	30 sube.					
17	30 sube.					
8	100 intrav.	T. 2°+	Resolution.			Patient alcoholic; acute delirium; edema of lungs. Serum without effect.
9	100 intrav.		Death 19th day. Temp. rose 4°; edema of linings.			
10	100 intrav.					
11	100 intrav.					
6	30 sube.	T. 2°—	Death.	Erythema 19th day	Abscess of scalp, otitis media twenty-first day, pyopneumothorax, 600 c.c. pus. Edema of lungs, twenty-fourth day.	Serum without any definite effect. Patient very ill on admission.
7	50 sube.	T. 3°—				
9	45 sube.					
11	50 sube.					
14	50 sube.					
3	100 intrav.		Recovery.	Urticaria fever 17th day.	Pleurisy with effusion 150 c.c. aspirated.	No definite effect of serum. Temperature fell by lysis after last injection.
4	100 intrav.					
5	100 intrav.					
5	100 intrav.					
6	150 intrav.					
7	200 intrav.					
4	100 intrav.	T. 2°—	Recovery.		Empyema. (Pneumococcus) operation.	Temperature fell gradually after first injection. No effect from later injections.
7	150 intrav.					
8	200 intrav.					
10	200 intrav.	T. 3°+				
6	200 intrav.	T. 3.5°—	Recovery.	Erythema 16th day.		Sharp drop in T., P. and R. immediately after serum.
3	80 intrav.	Edema of lungs in one-half hour.	Crisis 9th day. Recovery.	26th day. T. 104°; 27th arthritis.		Patient had symptoms of anaphylaxis. Serum stopped; no effect.
4	150 intrav.		Recovery.			Resolution fourth week; no effect from serum.
6	175 intrav.					
9	200 intrav.		Recovery.			Temperature fell by quick lysis after serum.

TABLE 1.—

Case No.	Sex,* Age in Years, Habits, Etc.	Condition of Patient				Blood-Culture, Etc.
		Day of Admission	Invasion	Temperature Pulse Respiration	Site Lesion	
11	♂ 39 Alcoholic	6		T. 104° P. 100 R. 36	L. U. L. L.	Pneumo- coccus
12	♂ 16 In extremis	2		T. 107°	R. L.	
13	♀ 2	5		T. 105° P. 136 R. 40	L. L.	
14	♂ 38 Alcoholic; third attack	6		T. 103.6° P. 124 R. 24	R. U.	
15	♂ 24	8 (?)		T. 105.4° P. 102 R. 32	R. L.	Sterile Plasmodium malariae
16	♂ 24	3	Chill	T. 105° P. 144 R. 40	L. L.	Sterile
17	♂ 4½	11	Chill, cough	T. 101° P. 118 R. 32	L. L.	
18	♂ 30 Alcoholic	6		T. 105° P. 128 R. 44	L. U.	
19	♂ 32	4	Chill	T. 104.6° P. 120 R. 44	L. L.	
20	♂ 13	3	Chill	T. 102° P. 120 R. 48	R. L.	Sterile
21	♂ 54	6	Chill	T. 104.8° P. 88 R. 24	R. U. R. L.	Sterile
22	♂ 20	5	Chill	T. 105.6° P. 120 R. 44	L. L.	
23	♂ 33 Alcoholic	4		T. 102.4° P. 100 R. 48	R. L.	

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Serum Administration			Outcome of Disease			
Day of Disease	Dose, Methods	Effect	Termination of Case	Serum Sickness and Day of Disease it Appeared	Complications	Remarks
6	200 intrav.		Death.			No effect of serum on T., P. and R. Died three days later.
3	150 intrav.		Death.			Died in eighteen hours.
8	100 intrav.		Crisis 12th day. Recovery.	Erythema 14th day.		No effect from serum. Crisis fourth day after serum.
6	150 intrav.	T. 2°—	Death.		E d e m a o f lungs.	Temperature rose steadily; died eleventh day.
9 11	250 intrav. 50 subc.	T. 4½°—	Death.			Temperature fell after first injection, but rose again and rose after second injection.
4 5	250 intrav. 50 subc.	T. 3°—	Death.			Temperature dropped after first injection and then rose. No effect of serum.
12	50 subc.	T. 2°—	Lysis. Recovery.			Temperature fell 2° and then to normal after serum.
6 9	250 intrav. 50 subc.		Lysis. Recovery.	13th day rash and fever; 16th arthritis.		Slow lysis interrupted by serum sickness.
4 7	250 intrav. 50 subc.		Lysis. Recovery.	Arthritis; fever 18th day.	Pleurisy with effusion; tenth day, 700 c.c. turbid serum; 12th, 350 c.c.; 25th, pus.	Serum without apparent effect.
4	250 intrav.	General pains.	Crisis 5th to 6th day. Recovery.	Urticaria after two hours.		Crisis twenty-four hours after serum.
8	300 intrav.		Lysis. Recovery.			Lysis rapid twenty-four hours after serum.
6	250 intrav.		Crisis 6th to 7th day. Recovery.			Crisis nine hours after serum.
5	200 intrav.	Nausea, vomiting, pulse rapid and sweating.	Crisis 6th day. Recovery.			Crisis twenty-four hours after serum.

tolerated surprisingly well. In five patients, however, symptoms appeared that should be mentioned more in detail.

CASE 1.—A boy aged 12, received 50 c.c. of serum intravenously on the fourth day of his illness. A few minutes later the patient had a chill and his temperature rose from 104 to 107.2 F. This was followed by a startling drop, and within six hours of the injection his temperature was 97.6 F. The fever did not reappear, and convalescence was prompt and complete. I am inclined to regard this crisis as independent of the treatment, but at the time the sequence of events was very impressive.

CASE 8.—The patient was a negro, aged 30, a rather heavy drinker and a driver of horses. When 80 c.c. of serum had run into the vein, he suddenly developed severe dyspnea, a very rapid and weak heart-action, profuse sweating and edema of the lungs. The serum was at once stopped. Within a few minutes the symptoms began to abate and within half an hour the lungs were nearly clear and his condition was satisfactory. The subsequent course of the pneumonia was typical and but moderately severe. Six days later, on the ninth day of the disease, defervescence by crisis occurred. Convalescence was interrupted only by symptoms of serum sickness.

CASE 20.—A boy aged 13, during the introduction of the serum complained of headache, pain in the abdomen and later in the legs. The pulse was accelerating and the serum was stopped, but not until he had received 200 c.c. Two hours later a profuse urticarial rash appeared on the abdomen and lasted a few hours. The patient had no late symptoms of serum-sickness.

CASE 23.—A man, aged 33, a heavy drinker, when 150 c.c. of serum had been given, became nauseated and vomited. These symptoms ceased in about five minutes and 50 c.c. more of serum were given. At this time the pulse became rapid and the patient broke out in a profuse sweat. The serum was stopped and in a few minutes he was comfortable. He likewise had no late serum symptoms.

The effect of the serum on the leukocytes was determined by frequent blood-counts before and after the injections. No constant effects on the white cells could be made out. The results of some of these counts are detailed in Table 2.

Late symptoms due to the serum were noticed in eight patients. In consideration of the large doses of unrefined horse-serum, this is not a surprisingly large number. The symptoms were not usually severe.

During the time of this experiment the First Medical Division of New York Hospital treated fifteen cases of pneumonia with six deaths, a mortality of 40 per cent., as compared with 30.5 per cent. for the serum cases. Of their ten cases with recovery, in six, or 60 per cent., there was defervescence by crisis. In the serum cases 50 per cent. of the patients who recovered had crisis. Only two of the control cases had complications, a percentage of 13.3. In the serum cases five patients, 22 per cent., had complicating inflammations. It does not seem that these were due to the use of the serum, but the number of patients with inflammations of the pleura (four cases, 17.4 per cent.) is uncomfortably large.

TABLE 2.—BLOOD-COUNTS BEFORE AND AFTER INJECTION

Case No.	Dose of Serum	Serum, c.c.	Leukocyte Counts					
			Before Serum		After Serum			
			No. of Cells	Percentage of Polynuclears	Hours After Serum	No. of Cells	Percentage of Polynuclears	Note
1	first	60*	25,000	86.5	2	19,000	85	} Crisis
					4	30,000	87	
					6	29,000	81	
					18	20,000	69.5	
					27	14,000	44.7	
2	first	30†	15,000	81.0	3	14,500	65	} Crisis
					5	12,700	70	
					14	10,500	76	
	third	30†	13,000	70.0	2	12,900	70	
					13	11,000	70	
					36	15,900	71	
3	first	100*	50,000	94.5	2	49,500	95	
					4	50,000	91	
					16	55,000	97	
5	first	100*	24,400	85.0	2	26,900	92.5	
					4	25,000	86	
					6	25,400	89	
					8	25,900	88	
					10	24,500	88	
6	first	100*	27,800	88.5	21	20,000	85	
					2	29,000	91.5	
					4	26,900	94	
					6	28,800	93	
10	first	200*	20,800	93.5	2	29,000	94	
					4	27,000	93	
					6	23,000	90	
					18	21,100		
16	first	250*	14,000	86.0	2	16,400	92	
					4	15,400	89	
					6	12,200	84	

* Intravenous injection. † Subcutaneous injection.

A study of the results of this treatment leaves one doubtful of the influence of the serum, in modifying favorably the course of the pneumonia.

The prosecution of this experimental study necessitated much extra work in the wards and laboratory. This was performed by the members of my house staff, Drs. Howard, Kutil, Alling and Wildman. I wish to thank them for their enthusiastic willingness, which made these observations possible.

NOTES ON SERUM, CULTURES, ETC.

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The serum was prepared by injecting a horse with pneumococci from varied sources. These cultures were all typical inulin fermenting types. They were

isolated from the mouth in cases of Riggs' disease, from the sputum in cases of lobar pneumonia, from empyema, and from the meninges and blood of septic infections following the exanthems. The cultures used varied from time to time. As fresh cultures were isolated the older cultures were dropped. No attempt was made to raise the virulence of these cultures by passage through rabbits or mice. Although this may influence the protective value of the serum for these animals, it is open to question what influence such adaptation to a new host has on the curative value in man. The cultivation on artificial medium undoubtedly changes the pneumococci, but how far this influences their ability to stimulate curative substances in the horse is unknown. The purpose was to prepare an immune serum against the prevailing strains of pneumococci, using the strains as little removed from human sources as possible; and to test the value of such serum for general use, where the immunological tests on each case would be impossible.

The injections at first were cultures in broth to which was added horse-blood. Later the cultures were grown on agar and washed off with water. At first the increasing doses were of cultures which had been heated to 55 C. for one hour. When the dose had reached the maximum decided on, live cultures alternating with autolysate were used. The autolysate was prepared by allowing distilled-water suspensions of the cocci to stand in the ice-chest for one week. The live cultures or the autolysate were added to the heated vaccine, in increasing amounts, until only the unheated culture or autolysate was given.

The injections were given once a week subcutaneously. The maximum dose equaled the growth on agar in 10-pint Blake bottles. The horse was receiving the total amount of live and autolyzed cocci at the time it was supplied to Dr. Williams. The bleedings were made every two weeks. Every effort was made to supply the fresh serum to avoid any possibility of deterioration. After the serum was drawn from the clot, several cubic centimeters of chloroform were added to each liter. In bottling the serum for use, the supernatant serum was drawn off and the lower portion containing sediment and excess of chloroform discarded.

The material from the cases was examined both for diagnosis, and in the hope that the cultures isolated could be studied for their complement-fixing power, with the serum used, and that the protection value of the serum could be tested on the type of pneumococci found. This study was not made, partly because of other work, and partly because the strains were found to possess such low virulence for rabbits. When the intravenous inoculation of the growth from one blood agar slant was given, only two strains killed, one in forty-eight hours, the other after ten days. Cultures isolated from the heart's blood of these rabbits did not kill other rabbits when a somewhat smaller dose was used. The sputum from Cases 18 to 23, inclusive, was examined. They all showed an overwhelming preponderance of typical pneumococci. One case of the series showed the presence of an abundance of *Streptococcus mucosus*.