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TREATMENT OF PNEUMONIA WITH PARTIALLY AUTOLYZED PNEUMOCOCCI *

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Rosenow has shown that when virulent pneumococci are suspended in physiologic salt solution the substance or substances on which their resistance to phagocytosis and virulence depend pass into solution.[1] The soluble part or "virulin" at a certain stage of autolysis is highly toxic and has little immunizing action, while the insoluble remnants have well-marked antigenic properties and practically no toxic effects. The soluble toxic part has been found to interfere with the formation of antibodies following injections of the non-toxic insoluble remnants. The protective value against experimental pneumococcus infections of detoxicated pneumococci has been found to be greater than that of heat-killed pneumococci.[2] For these reasons it seemed advisable to determine, if possible, whether or not the injection of virulent pneumococci, from which the readily soluble and toxic parts have been removed, would have any influence on the course and death-rate of lobar pneumonia.

PREPARATION OF ANTIGENS

The antigens or vaccines used during the winter of 1911, eight in all, were prepared from twenty-four-hour cultures of highly virulent pneumococci grown chiefly in ascites-dextrose broth. The broth was prepared from meat infusion, rendered sugar free, and then 0.2 per cent. dextrose was added and ascites fluid in the proportion of one part in ten. After centrifugation the pneumococci were suspended in 0.5 per cent. phenol in sodium chlorid solution and placed at 37 C. (98.6 F.) for twenty-four hours. This was repeated once or twice, until practically all the organisms had become Gram-negative and eosinophilous. Three of the antigens were prepared in the same way from the washed pneumococci which had grown in the peritoneal cavity of guinea-pigs. The antigens used during 1912 and 1913 were prepared from a large number of strains of highly virulent pneumococci which had grown both in the peritoneal cavity of guinea-pigs and in ascites-dextrose broth. The growth equivalent to that of approximately 150 c.c. of broth was suspended in 30 c.c. sodium chlorid solution at 37 C. under ether. In the case of the antigen used in 1912 the cocci were removed by centrifugation at the end of forty-eight hours and resuspended in sodium chlorid solution under ether. This was repeated twice. The disintegration was then marked and all the cocci had become Gram-negative. The antigen used during the winter of 1913 was prepared by suspending the pneumococci in sodium chlorid solution under ether at 37 C. until 7 c.c. of the suspension were no longer toxic for guinea-pigs when injected intravenously; that is, for about seventy-two hours. The organisms at this time had nearly all become Gram-negative. The sterility of the final product was determined by making both aerobic and anaerobic cultures on blood-agar. Some care must be exercised not to carry the process too far, because then all antigenic powers may be lost; experiments indicate that the best time to interrupt the lysis is when almost all the cocci have lost their affinity for the Gram stain. Standardized suspensions are used from the beginning of the extraction, and the final suspension represents about 20 billion pneumococci per cubic centimeter. This is kept in the ice-chest.

The dose used during the winter of 1911 varied from 10 to 20 billion. The injections were given subcutaneously daily until the temperature reached normal. During the second period, 1912, only one injection of approximately 20 billion was given as soon as the diagnosis was established, while during the past winter from 10 to 15 billion were given daily until the temperature reached normal. Only slight tenderness follows the injection and there is little local and no general reaction noticeable.

THE TREATMENT OF CASES

The cases treated may be considered in three classes: the cases treated outside of the hospital, the uncontrolled cases in the hospital and those controlled by alternate untreated cases.

The results in the thirty cases occurring in the practice of physicians outside of the hospital were better than those obtained in the more unfavorable cases in the hospital. Of the 30 patients, three died. One of these showed a large number of influenza bacilli in the sputum, together with pneumococci and streptococci; the second patient had a high grade of emphysema, due to a bronchial asthma of long standing, and the third death occurred in an alcoholic aged 58 who had a chronic myocarditis. Injections were begun in the fatal cases on the fifth, second and fifth day, respectively; in the patients who recovered, on the first or second day in seven, on the third day in eight, on the fourth day in five and on the fifth, sixth and seventh days in six; while in four cases the exact time of onset could not be ascertained. The ages ranged from 19 to 58 years. The results as determined by observation at the bedside when the treatment was begun within forty-eight hours of the onset often

* From the Memorial Institute for Infectious Diseases, Chicago.

1. Rosenow, E. C.: Human Pneumococcal Opsonin and Antiopsonic Substance in Virulent Pneumococci, Jour. Infect. Dis., 1907, iv, 285; abstr., THE JOURNAL A. M. A., July 6, 1907, p. 87. Tchistovitch and Yourevitch (Ann. de l'Inst. Pasteur, 1908, xxii, 611) made the same discovery.

2. See preliminary note by Rosenow, E. C.: Autolysis of Pneumococci and the Effect of the Injection of Autolyzed Pneumococci, THE JOURNAL A. M. A., June 11, 1910, p. 1943; Immunization in Pneumococcus Infections, Sept. 7, 1912, p. 795; Mechanism of Intoxication in Pneumococcus Anaphylaxis and in Pneumococcus Infections, Tr. Fifteenth Internat. Cong. Hyg. and Demog., 1912, ii, 338.

seemed striking: there was usually a rise of about a degree in temperature in a few hours, then the temperature would usually drop markedly, to remain one or two degrees lower the following day, and if now the injection was repeated, a normal temperature was often reached in three, four or five days after the onset. When the injections were given in three or four days after the onset the beneficial effect was less evident, while if begun still later there was no apparent improvement. Harmful effects have not been observed in any of the cases.

The second group, consisting of thirty-five cases, occurred in the Cook County Hospital during November and December, 1910. They were treated in the same manner as the cases just mentioned. Nine of these patients died, a death-rate of 25.7 per cent. The injections in the fatal cases were begun on the second day in only one case, on the third day in two, and in the remaining on the fourth, fifth and sixth days. One of these cases was found to be streptococcus pneumonia, in the other pneumonia developed during puerperal sepsis, and one patient had delirium tremens. Three others were bad alcoholics. The treatment in the cases with recovery was begun on the second day in two, on the third in three, on the fourth in three, and on the fifth, sixth, seventh and eighth days in the rest. The ages in this group ranged between 18 and 70 years.

We come now to the consideration of the third and largest group. The good effect of the early injections often seemed convincing, but because pneumonia is so variable in its course some sort of control is desirable. In order to do this most effectively we used the statistical method. Every second pneumonia patient in the order admitted to the Cook County Hospital of Chicago during January, February and March of 1911, 1912 and 1913, the height of each pneumonia season, was injected subcutaneously with detoxicated pneumococci at the same time as he received the usual routine treatment given to all patients with pneumonia, which was not modified in any way whatsoever. There was no selection practiced at all—every second pneumonia patient was injected, the uninjected serving as the control group. We are deeply indebted to the physicians of the hospital for their willing cooperation and encouragement. Altogether there are 294 cases for consideration in this group, 146 receiving the injections and 148 constituting the controls. Of the control group fifty-six died, a death-rate of 37.8 per cent. Of the injected group thirty-four died, a death-rate of 23.3 per cent., a total lowering of the death-rate of 14.5 per cent. in the injected group.

TABLE 1.—DEATH-RATE IN THE TREATED AND UNTREATED PNEUMONIA CASES BY YEARS

Year	Treated			Untreated		
	Total No.	No. Died	Death-Rate	Total No.	No. Died	Death-Rate
1911	51	16	31%	50	25	50%
1912	46	11	24%	48	15	31.2%
1913	49	7	14.3%	50	16	32%

Table 1 shows that the mortality-rate was lower in the injected than in the uninjected or control cases during each of the three pneumonia seasons. The unfavorable class of cases that we are dealing with is well illustrated by the very high death-rate of the control cases. It should be said at this time that the death-rate from pneumonia in Cook County Hospital is always very high because most of the pneumonia patients are of the least favorably situated class, hygienically and economically, of the whole adult male population of Chicago, many of them using alcohol excessively.

In Table 2 the death-rate is given by decennial periods. It shows a consistently lower death-rate in the injected cases than in the uninjected cases in each period except between the ages of 61 and 70 years. Here the mortality is slightly higher in the treated cases; but only four were treated with two deaths, whereas in the controls there were eleven cases with five deaths.

TABLE 2.—ANALYSIS OF THE RESULTS BY AGE-PERIODS

Decennial Periods	Treated			Untreated		
	Total No.	No. Died	Death-Rate	Total No.	No. Died	Death-Rate
1-20	21	0	0 %	17	2	11.4 %
21-30	39	7	18 %	36	8	22.2 %
31-40	43	11	25.5%	34	14	41.1 %
41-50	25	8	32 %	32	14	43.7 %
51-60	14	6	42.8%	18	13	72 %
61-70	4	2	50 %	11	5	45.45%
	146	34	23.3%	148	56	37.8 %

The incidence of complications and sequelae seems about the same in both groups, and the attack terminated by crisis of those that recovered in 71 per cent. of the injected and in 65 per cent. of the uninjected group. There is a tendency to earlier crisis in the injected group, especially in the cases in which there was a chance to begin the injections early. Thus during 1911 and 1913 when this point was studied, the injections were begun on the first or second day in all but two of the twenty-one cases in which crisis occurred on the sixth day or earlier.

Further analysis of the cases shows that the average age of the injected patients is 34 years while that for the uninjected patients is 36 years. The average age of the injected patients who died is 42.3 years, that of the uninjected patients who died is 42.9.

According to the facts obtained there were seventy-two bad alcoholics in the uninjected group and of these twenty died; there were seventy-three bad alcoholics in the injected group and of these twenty-six died.

The average duration of illness before entrance to the hospital in the control group is 4.3 days; of the control fatal cases 4.4 days; of the injected cases 3.9 days, and of the injected fatal cases 4.3 days. The first injection in nearly all cases was given the day after admission. This makes the average time of the first injection about the fifth day of the disease—necessarily a disadvantage in any form of treatment of pneumonia and particularly for the one under consideration.

CONCLUSIONS

In view of the fact that the mortality is consistently lower in the injected cases each year, that the average time of the first injection was late (approximately the fifth day), and that the type of cases treated is of the worst kind, nearly one-half of the patients being bad alcoholics, the conclusion that this method of treatment of pneumonia is of value seems warranted.

The results obtained in the series outside of the hospital, in which the injections were begun earlier, indicate that by the early administration of the antigen better results can be secured. Further observations require the cooperation of physicians who are in position to give the injections at the earliest moment.[3]

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3. The antigen or vaccine is kept on hand and it will be sent free on application to physicians who are willing to send us records of the cases.