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THE TREATMENT OF LOBAR PNEUMONIA WITH REFINED SPECIFIC ANTIBACTERIAL SERUM *

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The treatment of lobar pneumonia with a specific antibacterial serum has been under discussion for many years. It is now the opinion of those having no recent experience with the antibacterial serum that it is somewhat useful in type I cases, of doubtful value in type II cases, and useless in type III and group IV cases. All are agreed that the large doses of crude serum necessary to give sufficient antibody are a serious disadvantage. Recent investigations, however, have given us a more favorable outlook.

Seven years ago, at a meeting of the Influenza Commission of the Metropolitan Life Insurance Company, it was decided to make a serious attempt to determine the value and limitations of refined antibacterial serum and to stimulate attempts to improve it. The active members of the commission, McCoy, Jordan, Rosenau, Frost and Park, differing in their views from skepticism to optimism, were thought to be a suitable group for properly appraising the value of the serum.

Because of its large available material, Bellevue Hospital in New York was chosen as the main center for the test. Dr. McCoy assigned Dr. Cecil from the U. S. Public Health Service to take charge of the details of the investigations. The active cooperation of the attending physicians was readily obtained. The Cornell University Medical College assigned a portion of its laboratory for the pneumonia investigations. The cases of pneumonia were scattered throughout the wards of the four medical services.

The antibody solution prepared by Huntoon was chosen for the test and was supplied to the commission without charge. After three years of trial it was decided that, while its potency for types I and II was good, the chills and hyperpyrexia frequently caused by this antibody solution were too severe to make its further use in the hospital desirable. We therefore adopted the refined antibody solution which had just been prepared by Felton working under Rosenau at Harvard University. During the past three years Felton has greatly modified and improved his methods of eliminating inert and deleterious substances. For two years he has made a dependable product which retains almost the full strength of the serum antibodies of the original serum, with but little protein and almost no lipoid. At present 90 per cent of his preparations produce neither chill nor serum sickness and the other preparations produce reactions in only about 10 per cent of the patients. In 5 per cent of the cases slight allergic reactions develop, such as restlessness and moderate dyspnea, which soon pass off.

The results of the use of Felton's serum at Bellevue Hospital were recently reported by Dr. Cecil. The material which we are to consider in detail in this paper is that studied at Harlem Hospital where, owing to the generosity of Mr. Lucius N. Littauer and the cooperation of Dr. Lewis K. Neff, the medical director, it was possible two years ago to establish a separate pneumonia service under Drs. Bullowa and Rosenblüth. A resident physician and a staff of four bacteriologists and two chemists gave their full time to the investigations. This special staff and the large number of pneumonia patients made the conditions for evaluating the serum ideal.

The antibody solution used in these investigations was in major part prepared by Felton. Banzhaf and Sobotka of the health department and the Littauer Fund of New York University prepared antibody, using methods of precipitation and refinement different from Felton's. Their preparations are not yet as uniformly free of chill-producing substances as Felton's but have recently become sufficiently dependable for routine use.

All patients with lobar pneumonia admitted to Harlem Hospital receive identical treatment except that alternate patients are given serum. In order to compare cases of like severity, a system of numerical rating was devised which has been referred to elsewhere.[1] Blood cultures are taken immediately in all cases and sputum is collected as soon as possible for typing. The patients who are given serum receive doses of polyvalent serum containing approximately 10,000 units of type I and 10,000 units of type II and a much smaller amount of type III. These doses are repeated every eight hours while the temperature is above 102 F. As soon as the type is determined, the polyvalent serum is replaced by the appropriate monovalent serum. The nursing is the routine nursing of a municipal hospital with crowded wards. The patients were for the most part colored, with a high percentage of South and Central Americans recently domiciled in the city.

Except for the serum, the treatment of all patients is identical. This standard treatment stresses certain fea-

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* The investigation received financial support from the Littauer Pneumonia Fund, New York University, and the Influenza Commission Fund, Metropolitan Life Insurance Company.

1. Park, W. H., and Cooper, Georgia: Antipneumococcus Serum in Lobar Pneumonia, J. A. M. A. **90**:1349 (April 28) 1928. Rosenblüth, M. B.: Relation of Bacteremia in Lobar Pneumonia to Prognosis and Therapy, ibid., p. 1351. Bullowa, J. G. M.: Use of Antipneumococcic Refined Serum in Lobar Pneumonia, ibid. p. 1354.

tures: (1) adequate fluids up to 3,000 cc. daily; (2) no drastic catharsis; (3) restriction of the use of opiates; (4) relief of pleuritic pain by strapping with elastic adhesive plaster; (5) rapid digitalization for pulse rates over 120; (6) oxygen by tent or nasal catheter for cyanosis or rapid breathing.

Before commenting on the results in the 793 cases treated during the past two years in the Harlem Hospital, we believe it essential to consider a few tech-

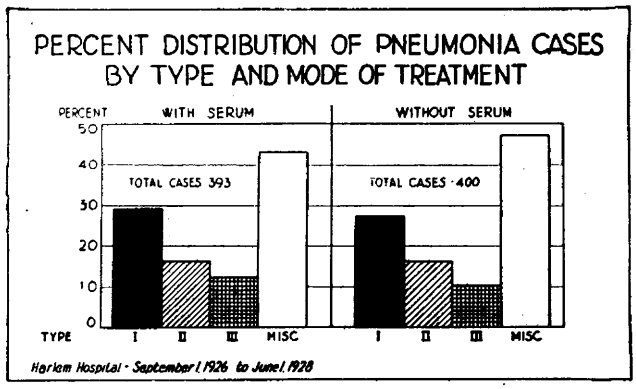

Chart 1.—Percentage distribution of pneumonia cases by type and mode of treatment in the Harlem Hospital from Sept. 1, 1926, to June 1, 1928.

nical points of vital importance in judging the present and future prospects of the use of serum antibodies in cases of pneumonia. It is well known that the pneumococci belong to different types and that it is necessary to match the infecting type in the case with its specific antibody. It is also necessary that the specific antibody be given in sufficient amount. At present only about 60 per cent of the pneumococci which cause pneumonia have been classified into types. The remaining 40 per cent are therefore unsuitable for serum treatment. This is one of the great drawbacks to the use of the antibody treatment. But this objection is now being lessened. Miss Cooper in the laboratory of the health department has discovered that more than 50 per cent of the pneumococci belonging to the miscellaneous group (group IV) fall into ten additional types, each of which is just as distinct as is type I, II or III, and each of which makes in animals a type specific antiserum. She did this by injecting a large number of rabbits each with a different one of a large number of group IV strains and then testing 120 strains against these immune serums. She regards atypical type II and atypical type III strains as belonging in group IV. These group IV strains were sent her from a number of hospitals.

The separation of a new type from pneumococci thought to be type III strains came about in a very interesting way. A study of the relation of freshly isolated type III strains to their antiserum was begun because concentrated refined antibody apparently of high titer as estimated by protection tests in mice against our virulent type III stock culture did not give the expected therapeutic results in the treatment of cases of type III pneumonia. Freshly isolated strains from cases, including some which failed to respond to serum treatment, were studied, and we were greatly disappointed to find that a type III antibody preparation which had 1,000 protective units per cubic centimeter against the type III stock strain had against freshly isolated strains only from 10 to 50 units. This failure to protect is believed by us to be due in part to the larger amount of capsular substance which these strains possess when in the body tissues or when freshly isolated. Miss Cooper also found these pneumococci with large capsules less suitable for the stimulation of antibodies. This disappointing discovery was offset by another encouraging one. Five strains were studied by Miss Cooper which agglutinated well in type III diagnostic serum but less well than typical type III strains. The agglutination was smaller in quantity in the lower dilutions and the floccules smaller in size in the higher dilutions. The titer was from one-fourth to one-half that of the typical strains. Three of the five strains had been classified at the Harlem Hospital as type III and two as probably of the miscellaneous or group IV type. Monovalent specific antiserums were prepared for the stock strains and two of the atypical strains. The antiserum for the stock type III strains which had 25 protective units per cubic centimeter against the freshly isolated typical type III strain did not show any protection against these atypical strains. An antiserum developed in the rabbit by injecting one of the atypical strains had 500 protective units per cubic centimeter against the atypical strains and only 1 unit per cubic centimeter against the freshly isolated type III strain.

The cross protection between the typical III strains and atypical strains is so slight that to include them in the same group seems unwarranted. Apparently effective antibody treatment in pneumonia as a result of these atypical type III strains could be carried out only with antiserum in which specific antibodies for this type had been developed.

The value of knowing that more than 50 per cent of the unclassified pneumococci belong to ten additional types is that we may now be enabled to produce specific protective antibodies against all these types and combine them as a polyvalent antibody. We are now injecting horses with them. We have already produced in horses potent specific antiserums against four of the new types. We hope finally to produce a polyvalent serum containing specific antibodies against all the thirteen types, so that it will be possible for the physician

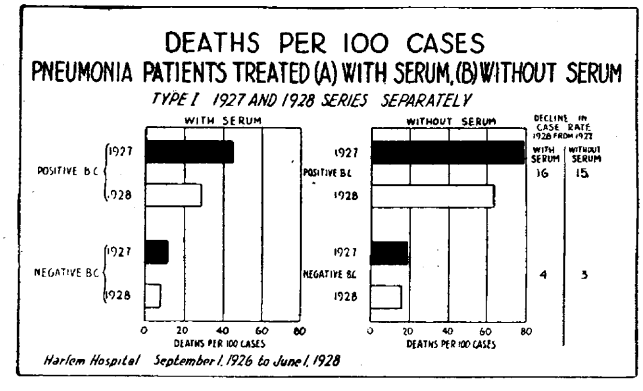

Chart 2.—Deaths per hundred cases in patients with type I pneumonia treated with and without serum in the Harlem Hospital from Sept. 1, 1926, to June 1, 1928; 1927 and 1928 series separately.

who does not have access to laboratories to treat his patients successfully without having the infecting pneumococcus typed.

There are a few points still necessary to touch on before the results of the treatment of pneumonia with the specific serum are discussed. In a previous paper [2]

2. Park, W. H., and Cooper, Georgia: Studies on the Leukocytes in Lobar Pneumonia: The Possibility of Rendering the Blood of Cases of Types I and II Lobar Pneumonia Antibacterial by Injections of Antibody Solutions, Tr. Sect. Path. & Physiol., A. M. A., 1927, p. 117.

we gave the results of tests showing that, in patients having type I pneumonia, the blood had only a moderate amount of soluble specific substance, while in those with type II infection there was sometimes a very large amount. This explained why in every case of type I pneumonia which we treated we were able to show free antibody in the blood soon after the treatment was begun, while in the late severe type II cases that was frequently not the case. This finding indicated that it was very important to give early treatment to persons with type II pneumonia and to give them more antibody than those with type I, and that in late severe cases of type II it may be impossible to give enough.

TABLE 1.—*Deaths per Hundred Cases in Pneumonia Patients Treated With Serum and Without Serum*

Experience of Harlem Hospital from Sept. 1, 1926, to June 1, 1928; 1926-1927 and 1927-1928 Series Separately

	With Serum			Without Serum		
	Cases	Deaths	Deaths per Hundred Cases	Cases	Deaths	Deaths per Hundred Cases
Type I						
Total cases *						
1927-1928	109	18	17	105†	33	31
1928	54	8	15	52	15	29
1927	55	10	18	53	18	34
Positive blood culture						
1927-1928	28	10	36	28	20	71
1928	17	5	29	14	9	64
1927	11	5	45	14	11	79
Negative blood culture						
1927-1928	80	8	10	74	13	18
1928	37	3	8	8	6	16
1927	43	5	12	36	7	19
Type II						
Total cases						
1927-1928	56	13	23	61†	18	30
1928	30	7	23	23	4	17
1927	26	6	23	38	14	37
Positive blood culture						
1927-1928	14	7	50	11	9	82
1928	9	4	44	1	..	..
1927	5	3	60	10	9	90
Negative blood culture						
1927-1928	42	6	14	47	9	19
1928	21	3	14	22	4	18
1927	21	3	14	25	5	20

* No blood culture was made in one case.
† Blood cultures were not made in three cases.

The last point we wish to emphasize is the importance of having not only a polyvalent antibody solution but one in which the strength of antibody for the different types is approximately known. Without this knowledge we shall be ignorant as to whether we are giving the desired amount of specific antibodies in any case of pneumonia we are treating.

RESULTS OBTAINED IN THE HARLEM HOSPITAL FROM THE USE OF THE ANTIBODY SOLUTION

Because of the importance of treating patients at the earliest moment it was impracticable to alternate them by type, since often at least twelve hours would have been lost before this was determined. Patients were therefore taken alternately for antibody treatment or control, depending only on the order of their admission to the service. It was believed that with a sufficiently large series the distribution of cases by type would be equalized between the treated and the untreated group. That this actually has been the case is seen in chart 1, which shows the percentage distribution by type in the two groups.

In two recent papers,[3] we reported the results obtained with the use of refined serum in the treatment of type I and type II lobar pneumonia during the first year of its use. In the present paper we bring our own statistics up to date, analyze them further, and combine them with those from Bellevue and New York hospitals.

3. Park and Cooper (footnote 1). Rosenblüth (footnote 1).

The invalidity of using the statistics of one year to control those of another year is shown in table 1 and chart 2. It will be seen there that in using type I cases we were able to demonstrate a diminished death rate during the season of 1928 from that of the season of 1927, in both the treated and the untreated cases, irrespective of the presence or absence of septicemia.

The table of the combined series (table 2) shows in type I cases at Bellevue Hospital a ratio of difference in case fatality to error of 2.6, while at the Harlem Hospital the figure was 2.4. When these statistics are combined and the figures from the New York Hospital are included, this ratio becomes 3.7. The New York Hospital figures are too small for separate statistical valuation. Since statisticians regard a ratio of difference for standard error of 2 as significant, the combined figure of almost double this is very impressive. It is important also to note the effect which increasing the size of the series has on raising the ratio and thus rendering more valid the appraisal of the therapeutic result.

In type II pneumonia the figures for Bellevue Hospital are significant but the combined experience is less so, because at the Harlem Hospital there was less difference in the serum and nonserum series. It should be noted that the death rate in the patients treated with serum at Harlem Hospital was less than at Bellevue Hospital—30 per cent as against 39 per cent—whereas in the untreated cases the death rate at Bellevue Hospital was 53 per cent, and at Harlem Hospital 32 per cent. The death rate for the untreated cases at Harlem was less than that of the treated cases at Bellevue. It chanced that in the season of 1928 there was only one bacteremic patient in the nonserum group at Harlem Hospital, whereas there were nine in the serum treated group there. This is another evidence of the value of serum in the bacteremic cases and also of the need of a large number of cases to make the series comparable.

TABLE 2.—*Deaths per Hundred Cases in Patients with Lobar Pneumonia Treated With Serum and Without Serum*

Experience of Bellevue, Harlem and New York Hospitals, 1927-1928

Type	Cases	Deaths	Deaths per Hundred Cases		Cases	Deaths	Deaths per Hundred Cases		Difference in Case Fatality (A-B)	Ratio of Difference to Its Error
Type I										
Combined experience	266	51	19	2.4	249	82	33	3.0	14	3.8	3.7
Bellevue Hospital	144	27	19	3.3	132	43	33	4.1	14	5.3	2.6
Harlem Hospital	114	23	20	3.7	109	37	34	4.5	14	5.8	2.4
New York Hospital	8	1	(13)		8	2	(25)		..	...	...
Type II										
Combined experience	176	61	35	3.6	165	74	45	3.9	10	5.3	1.9
Bellevue Hospital	107	42	39	4.7	95	50	53	5.1	14	6.9	2.0
Harlem Hospital	61	18	30	5.9	63	20	32	5.9	2	8.3	.2
Type III										
Combined experience	82	27	33	5.2	92	27	29	4.7	4	7.0	.6
Bellevue Hospital	32	12	38	8.6	52	14	27	6.2	11	10.6	1.0
Harlem Hospital	47	15	32	6.8	38	12	32	7.6	0	10.2	...
New York Hospital	3	..	..	...	2	1	(50)		..	....	..
Miscellaneous types										
Combined experience	313	76	24	2.4	324	83	26	2.4	2	3.4	.6
Bellevue Hospital	131	39	30	4.0	128	51	40	3.3	10	5.2	2.0
Harlem Hospital	171	35	20	3.1	190	28	15	2.6	5	4.0	1.8
New York Hospital	11	2	(18)		6	4	(67)		..	....	...

In chart 4 the cases, all of which are type I (the combined results are shown graphically in chart 3), are considered according to the severity rating which

was given to each on admission. Three groups were formed on the basis of whether the patient's condition was regarded as poor, fair or good. This was done in order that cases that were treated might be controlled by cases of like severity. In the "poor" group (rating less than 50) all the patients who were untreated died, whereas in the treated patients 64 per cent died—a difference in case fatality of 36. In this group the ratio of difference in case fatality to the standard error was 2.5.

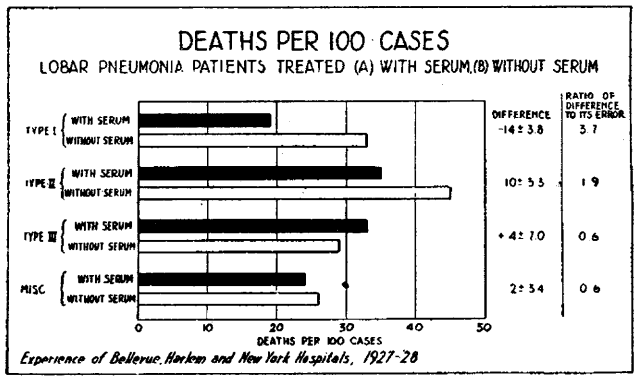

Chart 3.—Deaths per hundred cases in patients with lobar pneumonia treated with and without serum in Bellevue, Harlem and New York hospitals from 1927 to 1928.

In the "fair" group (rating from 70 to 50) 52 per cent of the patients without serum died, whereas 29 per cent of the treated patients died, a difference in the case fatality of 23.

In the "good" group (above 70) 13 per cent of the untreated patients died, whereas 9 per cent of those treated died, a difference in case fatality of 4.

It would appear, then, that the serum exerts its greatest effect in grave cases. This is probably because the incidence of bacteremia is greatest in such cases. Table 2 bears out this assumption.

Chart 5 separates patients into those with positive blood cultures and those with negative blood cultures. All type I and type II cases are included. In type I patients with positive blood cultures, 36 per cent of those treated with serum died, whereas 7 per cent of the untreated patients died. In those with negative blood cultures, 10 per cent treated with serum died, whereas 18 per cent of the untreated patients died.

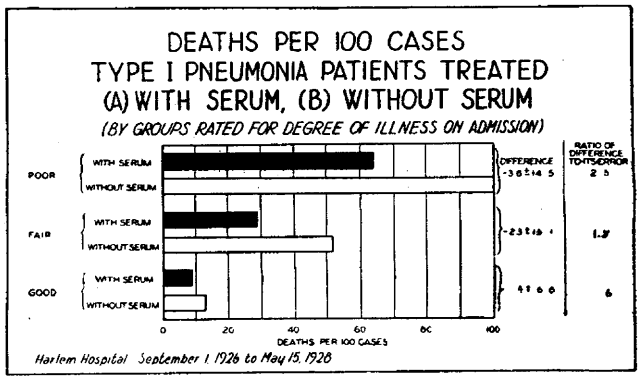

Chart 4.—Deaths per hundred cases in patients with type I pneumonia treated with and without serum by groups, rated for degree of illness on admission, in the Harlem Hospital from Sept. 1, 1926, to May 15, 1928.

In type II patients with positive blood cultures 50 per cent of those treated died, whereas 82 per cent of those not treated died.

In the type II patients with negative blood cultures 14 per cent of those treated died, whereas 19 per cent of those not treated died.

It is obvious from these figures that the serum is most needed in patients with bacteremia. This cannot be determined by clinical observation and, in order to treat such patients promptly, those chosen for treatment have had serum administered immediately after the blood was taken for a culture.

SUMMARY AND CONCLUSIONS

The fact that the introduction of a therapeutic dose of type I antibody solution into the vein of a pneumonia patient infected with the type I pneumococcus neutralizes all the soluble specific substance and leaves in the blood an excess of antibody would lead us to hope that its use would have a beneficial effect in lobar pneumonia. The lessened mortality of 42 per cent in lobar pneumonia at Harlem Hospital in a large series of cases treated with antibody, as contrasted with those untreated, is so great that, with the support of recent similar results at the Bellevue and New York hospitals, we consider that the value of the antibody in the treatment of type I cases of lobar pneumonia is proved.

When in a therapeutic test the ratio of difference in case fatality to its standard error is as great as 3.7, it is considered by expert statisticians to be conclusive proof.

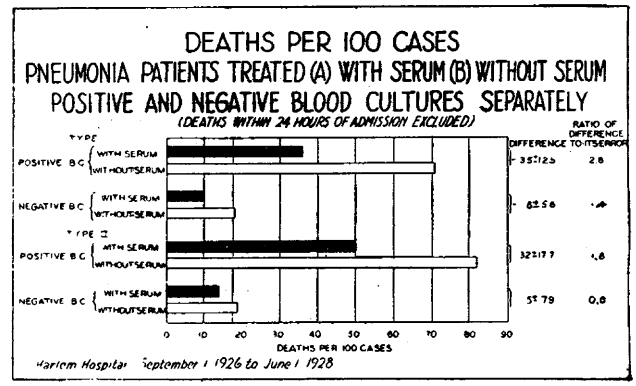

Chart 5.—Deaths per hundred cases in pneumonia patients treated with and without serum. The results in those with positive and negative blood cultures are shown separately. Deaths within twenty-four hours of admission are excluded.

In lobar pneumonia caused by type II pneumococci, we found that only in early cases would an ordinary therapeutic dose of antibody surely neutralize all the soluble type II specific substance. In late severe cases, especially those showing bacteremia, even repeated doses sometimes failed to do so. In the early cases, even when bacteremia had developed, the results were usually strikingly good. The mortality for the two years was 22 per cent less in the treated than in the untreated cases, and the ratio of difference in case fatality to the standard error was 1.9. While the evidence of the value of type II antibody is not as overwhelming as in the case of type I antibody, we believe that it is of very great value, especially if it is given early in the disease.

In the type III cases the specific antibody had only a slight effect in neutralizing the specific soluble substance and the therapeutic results were very slight, if any. Probably because of the excessive capsules which type III pneumococci have in or when freshly isolated from the body, the antibody has much less effect on freshly isolated than on virulent stock cultures. There is also another reason in that a fair proportion of sup-

posed type III pneumococci are a subtype which really belong to the miscellaneous (IV) group, just as do the subtypes A and B of type II. These pneumococci are influenced only slightly by specific type III or specific type II antibody, but are influenced strongly by their own specific antibody.

More than 50 per cent of the miscellaneous or group IV pneumococci, which form about 40 per cent of the whole, have been split up by Miss Cooper into ten types which are just as distinct from each other as are types I, II and III. We have prepared potent antibody for the majority of these and hope we can prepare a polyvalent antibody solution for them.

The results of the work of Felton, and to a lesser extent of Banzhaf and Sobotka, have put at our disposal a potent refined antibody solution for types I and II which has no apparent deleterious effect in the majority of persons suffering from lobar pneumonia and which has a potency of from five to ten times that of the unrefined serum. When horses are selected which produce a highly potent polyvalent serum, the first refined product has a very high titer. We are now able therefore to benefit about 50 per cent of the patients without accompanying deleterious effects. If our attempts to develop an antibody solution for one half of the group IV patients succeed, we shall be able by adding this to the polyvalent type I and II antibody to treat hopefully 70 per cent of all cases. The fact that it is the cases of bacteremia which apparently show the greatest improvement from the antibody solution is strong evidence of its value. The time has arrived when the biologic plants should undertake the production of the refined polyvalent pneumococcus antibody solution by the method of Felton or that of Banzhaf, or by a better one if it can be developed.

The Hygienic Laboratory should insist that the potency of the antibody solution be clearly stated for the different types for which the preparation is offered.

ABSTRACT OF DISCUSSION

DR. RUSSELL L. CECIL, New York: The serum with which we have been working in the treatment of pneumonia is not an antitoxin. It is an antibacterial serum which we give in the hope of helping nature overcome the pneumococci in the blood. The pneumonia patient who dies is usually septic, and the object of serum treatment is to produce an antibacterial rather than an antitoxic effect. During the past two years we have treated about 450 cases with an equal number of controls. The serum was always given as soon as the diagnosis was made without waiting for the type, but typing was done in every case by the mouse method. Our death rate in 150 type I cases treated was cut to about one-half that for an equal number of controls. In the type II group, 100 treated cases showed a death rate 25 per cent lower than that of the controls. In the type III and the type IV groups, there was very little to be seen as far as therapeutic effect was concerned. We have been successful in treating monkeys with this concentrated serum. Concentrated serum even in small amounts controls otherwise fatal pneumonia in monkeys, both in type I and type II infections. After a number of years of experience with these various specific agents for the treatment of pneumonia, we feel that in Felton's serum we have the best product that we have so far used. It is polyvalent. It is also highly potent, so that doses of from 10 to 20 cc. are equivalent to several hundred cubic centimeters of the old standard serums, and potency is needed, because we are dealing with a massive infection. How different the pneumonic lung is from the small foci of infection present in diphtheria and scarlet fever. We need a great deal of help for the patient because of the size of the infection. Felton's serum is a stable product. It keeps well. Another advantage is that reactions are rare. We have encountered two kinds of reactions, thermal and allergic. The thermal reactions are nothing more than foreign protein reactions, a chill with a rise in temperature. It has occurred in about 10 per cent of our cases but has been confined largely to certain lots of serum. Even when the chill does occur, it is not of a severe nature. The allergic reactions have been much less frequent than with regular serum because there is less protein injected. Serum sickness occurred in 15 per cent of cases and was never very severe. Felton's serum is efficacious. We have great hopes for this product.

DR. WILLIAM H. ROBEY, Boston: We have used the antibody solution for four years under the direction of Dr. Park and the pneumonia commission. The incidence of pneumonia is lower in Boston than in New York, and it is decreasing. We had seventy treated cases and seventy untreated cases, all type I, and all treated within the first three days. The mortality in those two groups was exactly the same. This failure has led to the abandonment to a certain extent of typing. In fact, typing is so little required by the physicians of the state of Massachusetts that the state board of health is considering giving up the opportunities for typing. Our treatment of cases at the Boston City Hospital, although in much smaller numbers, corresponds very nearly with the results of Drs. Park and Bullowa at the Harlem Hospital and of Dr. Cecil at Bellevue Hospital. Our results in using Felton's serum in cases treated during the first four days of the disease were as follows: In the type I group, among thirty-one cases, there was one death, a mortality of 3.2 per cent. Among twenty-six untreated cases, there were eight deaths, a mortality of 30.7 per cent. In the type II group, there were twenty treated cases with five deaths, a mortality of 25 per cent, and twelve cases untreated, with three deaths, a mortality of 25 per cent. In the type II group, there were four cases with one death, a 25 per cent mortality; among seven untreated cases there was one death, or 14.3 per cent mortality. In type IV, there were thirty-one cases with a mortality of 6.4 per cent, and twenty-nine untreated cases with a mortality of 17.2 per cent. Twenty patients were seen and treated after the first four days in the type I group, with a mortality of 30 per cent; in thirty-three untreated cases there was a mortality of 18.2 per cent. One of the most striking features in our observations is that in the cases of more than four days' duration, or particularly more than three days, it is almost impossible to reduce the bacteremia. In type 2, the mortality was extremely high; namely, fourteen cases treated, with a mortality of 35.7 per cent; in the untreated cases the mortality was 38.8 per cent. In type 3, there were five cases and one death, a mortality of 20 per cent, and eleven cases untreated with seven deaths, a mortality of 26.6 per cent. In type IV, there were thirty cases, with three deaths, a mortality of 10 per cent, and forty-five untreated cases, with seven deaths, 15.5 per cent mortality. In other words, our greatest results are in the type I cases treated within the first three days. Our next best results, which are more favorable than with any former treatment, are in type II cases. In types III and IV, we naturally feel that no result has occurred.

DR. W. H. PARK, New York: The potency of an antiserum depends on the reaction of the individual horse and the nature and the method of using the antigen. Its polyvalence depends on the number of antigens used. It may be interesting to know that at least two biologic plants have become so much interested in the antibody studies that they are planning to produce the pneumonia antiserum in large quantities and hope to have refined polyvalent serum that will not produce chills on the market in the fall. I am not sure that they will succeed, but the serum will be tested out thoroughly before it is put on the market. With regard to the treatment of early and late cases, we felt very strongly, as Dr. Tobey did, that only early cases should be treated, until about a year ago, when, because of animal tests, we felt more hopeful and began to give large doses of antibody in cases seen on the fourth, fifth or sixth day. A number of these patients who had shown a slight bacteremia recovered after the use of the antiserum. Our statistics for the last year are quite a little better for the late cases which were treated than for those left untreated. This was especially true for type I cases but also to a lesser degree for type II. While, therefore, we should try our best to treat the cases early with antibody, we should not withhold large doses

of serum from type I and type II patients who come for treatment rather late in the attack, if they are not too desperately ill. As Dr. Robey said, it is very difficult to draw accurate conclusions with small numbers. For instance, this year at Harlem Hospital there was almost the same mortality in our treated type II cases as in the untreated cases. It just happened this year that every case of type II bacteremia was on the treated side. When we put the figures for the two years together, the mortality for the treated cases was much better. We believe that the total cases reported from the three hospitals give us a sufficiently large number of cases to estimate the value of the antibody solution.

TINNITUS AURIUM

ITS INCIDENCE IN ENDOCRINE DISORDERS *

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In tinnitus aurium there is a close relation between the character of subjective noise and the underlying cause. Treatment is unfavorable when the noises do not vary in intensity and are continuous, is less so when they vary and are intermittent, and is favorable when they are altered or relieved by inflation. Analysis of 1,000 cases studied at the Evans Memorial, 585 of which were demonstrably endocrine, showed an incidence of tinnitus in 35.6 per cent of the endocrine cases and 32.7 per cent in the nonendocrine cases. Further analysis of the nonendocrine group showed an appreciable percentage of diseases in which tinnitus is a characteristic or frequent symptom. It is concluded that while tinnitus aurium is not a characteristic symptom of ductless glandular disorders, it is encountered equally often in hypofunction of all the endocrine glands.

Tinnitus aurium is a term employed to designate certain subjective sensations of ringing, roaring, ticking and whirring noises in the ear. It is a very common and often a distressing symptom. In fact, of all the symptoms which an aurist is called on to relieve, tinnitus is the most elusive and the most difficult to control. It may be caused by any form of tympanic or labyrinthine disease, and may result from other conditions not dependent on disease of the auditory apparatus. Again, we may cure the ear condition but absolutely fail to control the remaining tinnitus aurium.

A high pitched tinnitus (singing, hissing, chirping) indicates increased tension in the middle ear and is due to pressure on the stapes, active or passive hyperemia, or acute or chronic catarrh. A low pitched tinnitus (rushing, humming, shell-like) is usually vascular or muscular, and is especially perceptible when the resonance is increased by cerumen, collections of mucus or polypi. When pulsating, it is due to arterial congestion of the middle ear or labyrinth. Pulsating tinnitus is more frequent than patients would lead one to believe from their descriptions.

When relieved by pressure on the carotid artery, the congestion may be localized, as in the middle ear; when pressure on the vertebral artery (made by digital compression over the suboccipital triangle) diminishes the congestion, the internal ear is probably the part affected. Pulsating tinnitus is due very often to abnormal conditions of the ear, by which the pulsations of the heart or arteries, usually inaudible, become apprehensible. Although cases have been recorded in this connection wherein the tinnitus was audible, it should be remembered that the murmur of a thoracic aneurysm may be heard by the sufferer with distressing acuteness. A rushing tinnitus is due usually to venous congestion, is worse on lying down, and may be relieved by purgation. Deep humming, which is lessened on assuming the recumbent position or on taking food, is dependent on anemia. Scraping, crackling, rattling and gurgling are usually due to the movements of exudates in the middle ear.

It must be borne in mind that tinnitus may occur independently of ear disease, and the latter can be excluded only by a careful and thorough examination of the organ of hearing. It may be noted here that when tinnitus is persistent and out of all proportion to the ear condition, the urine should be examined for albumin and casts. Finally, in investigating cases of tinnitus, inquiry should always be made as to the period, in relation to other symptoms, at which the noises appeared.

In the great majority of cases, subjective noises are localized in the ear itself, but in many instances they are experienced within the head, in the occiput, in the temporal region or on the vertex. Intense noises, which occur in paroxysms, often extend from the ear to the inner portion of the head, and spread sometimes to the frontal and sometimes to the occipital region. It rarely happens that the sensation of sound is projected outward. This is especially the case, however, in the beginning of the disease when the subjective sensations are erroneously mistaken for objective noises, until experience corrects this phenomenon and rectifies the false conception.

Frequently only one kind of subjective noise is heard; occasionally, however, they change, or the most varied kinds of noises are perceived simultaneously. The intensity of the subjective noises is seldom uniform, and there are usually marked variations, which depend on the disease process itself but more often on external influences or on physical conditions.

Some of the external influences which produce an increase in the subjective noises are changes of weather and confinement in close, damp or smoky rooms. In the open air the noises are less annoying. Marked tinnitus is often forgotten because of diversion and occupation, which explains why many persons do not hear the noises during the day, while they become distinctly audible by closure of the external ear canal in quiet rooms and at night before going to sleep. Marked objective noises often overshadow the subjective ones so completely that persons on trains and in noisy rooms do not perceive the intense ringing in the ears. This, however, makes the latter appear so much the louder when the environment becomes quiet again. I have seen persons, however, who still heard subjective noises in the midst of the greatest uproar, while riding in the train and while listening to the performance of an orchestra.

It is frequently noticed that subjective noises are often produced or permanently increased by a temporary alteration of the condition of the general system. Bodily and mental exertions, conditions of the mind (epilepsy, in which the noise in the head may precede a seizure), continuance in a stooping position, excessive talking, coughing and sneezing, movements of the jaw in chewing, turning and shaking the head, sleeplessness or too much sleep, smoking, overeating, pregnancy and, in fact, all things which tend to produce an irritation

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