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*A Symposium on the Use of Antipneumococcic Refined
Serum in Lobar Pneumonia¹, December 15, 1927*

I

THE CONTROL

(ABSTRACT)

JESSE G. M. BULLOWA

A. THE IMPORTANCE OF A CONTROL SERIES OF CASES²

The evaluation of the effect of any therapeutic procedure in pneumonia is attended by certain inherent difficulties. Probably seven of every ten patients recover regardless of treatment, and therefore if one chances upon a succession of favorable cases, he is apt to attribute the benefit to the special treatment then in use. A short series of fatalities, unless carefully controlled and analyzed, may lead to a condemnation of what is really a very useful procedure.

Refined concentrated serum is desirable in order that the dose may be small and readily administered without severe reactions. It is desirable that it be polyvalent (several sera may be mixed) because the pneumonias resulting from pneumococci of different serological types may be indistinguishable at the onset. Because no one can foretell with certainty the cases which may develop adequate protection in response to the pneumonic invasion, the benefit from treating patients is best discovered by comparing the results in a series of serum treated cases with a similar series treated without serum.

At Harlem Hospital each alternate patient with pneumonia is placed in the serum series. It is not practicable

¹ These researches were financed by Mr. Lucius N. Littauer through the Littauer Pneumonia Fund of New York University in association with the Influenza Commission of the Metropolitan Life Insurance Company and the Research Laboratory of the Department of Health, New York, N. Y.

² The clinical studies are from the Medical Service, Harlem Hospital, Dr. Lewis K. Neff, Director.

Dr. Louis I. Dublin and the staff of the Statistical Bureau, Metropolitan Life Insurance Company, tabulated the data.

to alternate the cases according to type on admission as this might occasion a delay of many hours or days. The injection of a powerful polyvalent serum of Types I, II and of a less potent Type III assures prompt treatment of the cases selected for serum.

We accept and retain as pneumonia patients those having pneumococcus infections of the lung with definite lobar involvement, as evidenced by unmistakable physical signs, fluoroscopy, or radiography.

Except for the serum, all patients are given the same medical care in respect to drugs and nursing, in accordance with a definite plan.

B. DATA NECESSARY ABOUT THE CASES BEFORE ONE IS CAPABLE OF JUDGING THE EFFECT OF SERUM

On admission cases are rated in accordance with a definite plan. The rating assumes 100 to be health and for each of five categories a maximum of 20 may be subtracted.

Respiratory: Involvement. Rate. Pleurisy.

Nervous Condition: Headache. Irritability. Sleeplessness. Delirium. Apathy. Coma.

Circulatory Efficiency: Rate. Cyanosis.

Gastrointestinal: Distension. Vomiting.

Complications. Special Factors.

In our series studied during the past year we had 401 cases of lobar pneumonia, of which 28 were rejected because it was impossible to type them, and 8 because of concurrent febrile diseases, such as scarlet fever, tuberculosis, etc.; 365 remain to be studied, 169 in the serum series and 196 in the controls; 220 were rated.

In a general way the rating on admission indicated chances for recovery. The Type I cases treated were sufficiently numerous to classify as good, fair and poor. Chart (5). Of 6 patients rated poor (below 50) we saved 2 patients with serum, while we lost all treated without serum;

of those rated fair (50 to 70), we saved 4 of 6 in the serum group against 6 among 11 without serum. We saved with serum some very ill patients who might have died without it.

Many have maintained that the excellent results reported with serum treatment in hospitals have been due to the early hospitalization rather than to the serum. For both Type I and Type II serum series the mortality among both early and late cases was less than for the controls.

Not only did the serum treatment appear to reduce the number of deaths but it shortened the illness of those who recovered. Certainly this was advantageous, as it meant a saving in hospital care and of subsequent invalidism.

With serum we not only saved more patients and shortened the illness of those who recovered, but apparently the serum delayed death in those who perished, just as occurs in animal experiments.

When we combine all the cases early and late by types, and study the effect of the serum, it will be noted that Type I and Type II for which we had potent sera, showed fewer deaths per hundred among the serum treated cases. The greater benefit from early treatment has been revealed on charts already shown.

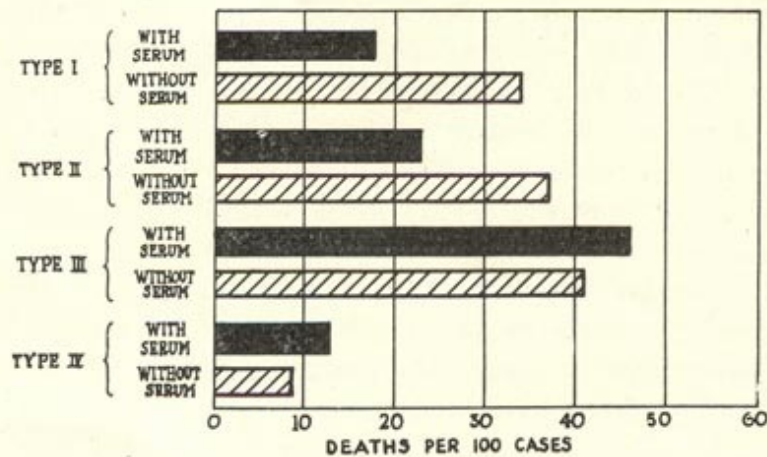
C. SIZE OF SERIES REQUISITE

Naturally, as physicians, we considered how long we were justified in continuing to deprive patients in the control series of what may be a valuable and available therapeutic aid. In spite of the fact that we were impressed, as the research proceeded, by the beneficial results of the serum, the question arose as to whether there was conclusive proof that the serum is of value. What test can we apply to our data to see whether proof is adequate and how can we determine the number of cases necessary for a judgment? This leads us into a brief digression into what differences in results is statistically significant, and the meaning of the standard error.

Without going into technical details, it may be explained that the relative spread, or flatness, of the curve of occurrence of a quality is measured by what is called the standard error of the measurements. In order that the difference between measurements in two separate materials, *e.g.*, case fatality of two similar hospital populations with pneumonia, one of which received serum, shall be recognized as definitely significant, the distance between the peaks of the two curves must satisfy a certain statistical test. The difference between the average measurements in the two cases must be at least equal to twice the "standard error" of the difference. Whenever this ratio falls below 2, we are not in a position to judge whether any significant meaning is to be attached to the difference.

Deaths per 100 cases
Pneumonia patients treated (A) with Serum and
(B) without Serum
Harlem Hospital, September, 1926 to October, 1927
DEATHS WITHIN 24 HOURS OF ADMISSION EXCLUDED

Type	(a) WITH SERUM			(b) WITHOUT SERUM			Difference in Case Fatality (a-b)	Ratio of Difference to its Error
	Cases	Deaths	Deaths per 100 Cases	Cases	Deaths	Deaths per 100 Cases		
Type I	55	10	18 \pm 5.2	53	18	34 \pm 6.5	-16 \pm 8.3	1.9
Type II	26	6	23 \pm 8.3	38	14	37 \pm 7.8	-14 \pm 11.4	1.2
Type III	24	11	46 \pm 10.2	17	7	41 \pm 11.9	5 \pm 15.7	.3
Type IV	54	7	13 \pm 4.6	82	7	9 \pm 3.2	4 \pm 5.6	.7



In the Type I cases we have practically obtained a result which is twice the standard error, 1.9. A greater difference in the percentage recovery of treated cases than those untreated may be accomplished by future improvements in the serum, and by earlier administration. Even though the serum were to remain as it is and the difference in the results the same as at present, 16 per cent., a greater number of cases would reduce the standard error and carry conviction of the value of serum treatment. When, for Type I pneumonia, the ratio of the difference in per cent. fatality between serum and non-serum treated cases to its standard error, becomes more than two or three, it will be our duty to administer serum in all Type I cases and urge its administration on others.

To evaluate the result of a treatment in pneumonia, there are required adequate comparable series with and without the treatment. We believe we have obtained such series by the devices adopted—alternating patients and rating them on admission. The size of the series requisite is determined by a consideration of the standard error.
