TREATMENT OF INFLUENZA-PNEUMONIA BY USE OF CONVALESCENT HUMAN SERUM.

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ON September 28th, 1918, serum from convalescent influenzal pneumonia patients was used at my suggestion, in the treatment of this type of broncho-pneumonias at the Chelsea Naval Hospital on the service of Lt. Comm. McGuire. The outcome in the treatment of 151 such cases has already been reported in the *Journal of the American Medical Association*,[1] where details of the procedure are given in full.

It is now my purpose to present the results of similar treatment in 100 cases in private practice.

At the time of the first report it was considered impracticable to do this type of work outside of a hospital. However, during the early part of December the demand for such treatment became so urgent that I, with my assistant, Mr. Arno, undertook the work of obtaining serum from civilians and of treating all cases which came to my attention, whenever I had serum. May I say in passing that I have never had a patient, either in the Naval Hospital or outside, who did not willingly give me all the blood I requested. In fact, they all considered it an honor to be able to help.

This report necessarily differs from those preceding, chiefly because all but five or six of these cases were seen from two to five days later in the disease than those at the Naval Hospital, where the majority of the cases developed the pneumonic complication on the wards and were given serum within the first twenty-four hours of the appearance of definite lung signs. The reason for the delay was due mainly to the fact that many of the physicians did not wish to have serum given when a patient appeared to be taking care of the disease without its help.

The diagnosis was usually established by the clinical influenzal onset of high temperature, headache, and a varying amount of pains and aches, and a low white blood count, followed in a few days by chest signs, either with or without intervening normal temperature. I have omitted several cases where lung signs were doubtful, so that this group includes only those showing definite signs of lung involvement. All but four cases were seen by at least two, and about one-fourth by three physicians.

The data are summarized in the following tables.

TABLE I.—PERSISTENCE OF FEVER AFTER FIRST INJECTION OF SERUM.

Normal in 24 hours or less	42
Normal in 58 hours or less	33
Normal in 72 hours or less	8
Normal in four days +	1
	84

Table I shows that the temperature in almost one-half of the cases dropped to normal within twenty-four hours of the first injection of serum, and that in three-quarters the temperature was normal within forty-eight hours. This, to me, indicates a decided shortening of the course of the disease.

TABLE II.—NUMBER OF INJECTIONS EACH PATIENT RECEIVED.

NUMBER OF INJECTIONS	NUMBER OF PATIENTS
1	52
2	35
3	8
4	3
5	2
	100

The average amount of serum given at each injection was 120 c.c.

Table II shows that over half the cases treated required only one dose of serum, and that over three-quarters required only two doses or less, which would seem to indicate that the 120 c.c. dosage was sufficient. It should be remembered that 120 c.c. represents only 100 c.c. of serum and that the remainder is salt solution in which the 0.30 per cent. trikresol is made up.

Of this group 76 had a white blood count either normal or below. The lowest was between 2500 and 3000. This was without regard to the time in the disease when first seen.

A group of 13 women advanced at least five months in pregnancy is also included. Of this number 3 died, or 23 per cent. Reports from clinicians who have dealt with large groups of pregnant cases show considerably higher percentages. For example, Woolston and Conley[2] had 52 deaths out of 101 pregnant cases, or a mortality of 51.4 per cent. And Harris[3] reported a mortality of 54 per cent. in a group of 678 pregnant women. It would appear, therefore, that even in pregnancy cases the serum helped to lower the mortality.

The total number of deaths out of 100 cases reaches a maxim of 16, or 16 per cent., which is four times that obtained in the Naval Hos-

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pital group. But a mere statement of mortality conveys an impression just as erroneous as if one gives statistics on diphtheria antitoxin when used on the third or fourth day of the disease, or on the use of anti-pneumococcus serum Type I in late or moribund cases. In other words, although the use of the serum has frequently seemed to do wonders, yet those accustomed to serum therapy recognize the importance of early administration, and know only too well that certain processes reach a stage irreversible by any procedure, or treatment. In order, therefore, to gain a correct conception of the mortality in this group, it is necessary to give a summary of the type of cases which died. Hence the following table.

TABLE III.—SUMMARY OF FATAL CASES.

Case Number	Age	Condition when Serum was First Given	Day of Pneu.	Time of Death after First Treatment
11	23	Moribund	6	4 hours.
25	27	Severely sick	7	2 wks. 200 c.c. pus removed from pericardium. Died 14 hours later
31	45	Moribund	6	6 hours
38	32	Cyanotic	7	14 hours
46	30	Pregnant, moribund	5	2 hours
50	50	(Poor condition, weighed about 280 pounds)	3	Normal in 18 hrs., remained so for 3 days, sat up suddenly, dropped back dead. Card. failure
55	28	Moribund	8	2 hours
56	30	Moribund	5	5 hours
58	30	Pregnant, cyanotic, irrational	4	3 dys. Ran normal temp. all 3 days, but grew constantly worse
60	45	Moribund	7	30 minutes
64	60	Cyanotic, irrational	6	18 hours
76	33	Pregnant, cyanotic	4	Temp. normal in 12 hrs. but grew rapidly worse
78	30	Severely ill	2	28 hrs. Given 3 doses of serum with no effect
87	28	Moribund	5-6	12-16 hours
89	27	Cyanotic, moribund	5	18 hours
93	28	Moribund.	5-6	12 hours

It is evident from the above that the condition of certain patients did not warrant the use of serum, except as a last resort and then chiefly as a consolation to the rest of the family. For example, cases 11, 31 38, 46, 55, 56, 60, 64, 76, 87, 93, where the first administration of serum was on the fourth day of the pneumonic involvement, or later, or where the patient was practically moribund, as indicated by the fact that death occurred in such a short time after the first visit, a time varying from ½ hour to 35 hours. Case 25 died of hemolytic streptococcus empyema of the pericardium, two weeks after the first administration of serum. Furthermore, case 50 had a normal temperature, pulse, and respiration for 3 days after the first dose of serum, then in an effort to sit up, dropped back onto the bed dead. She was a woman weighing 280 pounds, and in all probability died of acute dilation of the heart.

Therefore, by excluding the cases where the serum was given too late in the disease, and also those who died of complications other than pneumonia, there remain only 3 deaths, or a minimum mortality of 3 per cent. In all probability a just estimate of the efficacy of the serum lies between 3 and 16 per cent.

I now wish to review briefly the work of other observers along the same general line. This includes the use of whole blood, and plasma, as well as just serum separated from the clot. Ross and Hund[4] at Mare Island, California, treated 28 cases by transfusion and ran a control group of 21 similar cases untreated by this method. In the untreated group the mortality was 42.8 per cent., whereas the treated group showed only 21.4 per cent.

Brown and Sweet[5] treated 2 cases of marked broncho-pneumonia by transfusion with excellent results.

MacLachlan and Fetter[6] have reported 54 cases treated by use of citrated blood from convalescent cases. Of this group 34 recovered and 20 died, a mortality of 27 per cent. They suggest the exclusion of 7 cases moribund at the time of first treatment. This would leave 13 deaths, or a mortality of 24 per cent.

The criticism I wish to make in regard to this work is that patients received the blood of only one convalescent at each dose, and since I have shown that about 15 per cent. of such convalescent sera are inactive, there is a fair chance that a number of the treated cases were given blood of no potency. Furthermore, MacLachlan and Fetter used a dosage of only 100 c.c. of whole citrated blood, which would mean about 60 c.c. of serum, a dosage entirely too small, especially in severe cases. Moreover, I have found in the cases at the Naval Hospital as well as in the severer cases in private practice, that better results are obtained by giving at least 2 doses

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within a 24-hour period. For example, in one desperately severe case with a bad mitral disease, I gave 750 c.c. of serum in five doses, within 48 hours, with a favorable result.

In addition, this method necessitates careful blood grouping, hence a delay in administration and difficulty in pooling blood from four or five cases. Fortunately, when the work at Chelsea was started we had from thirty to forty donors so that, even when we did not use pooled serum, we readily found plenty of donors whose serum had demonstrated potency. Hence practically none of the earlier cases went without receiving an effective serum within 24 hours of the first injection when that proved worthless.

This brings me to the consideration of the work done by Hartman and O'Malley[7] at the U. S. Naval Hospital, Washington, D. C. As soon as our work at Chelsea came to the attention of Admiral Stitt, he wired for all details of technic. These were furnished by me through my commanding officer. Then the work with plasma from convalescent patients was instituted. The choice of plasma was due chiefly to the fact that Dr. Hartman had devised a simple method for transfusion, which was easily adaptable to the preparation of citrated plasma. These observers pooled the plasma, therefore their work is more comparable to that done at Chelsea, than that in which whole blood from single donors was used. Hartman and O'Malley report 111 untreated cases, with 28 deaths, or a mortality of 25.2 per cent., whereas a group of 46 cases, treated with the pooled plasma, showed only 3 deaths, or a mortality of 6.5 per cent. They further report that treatment in all 3 fatal cases was begun late. Their conclusions are: that the toxemia of influenza seems to be neutralized by the plasma of convalescent patients, that a large percentage of this plasma is active, but that most satisfactory results are obtained by pooling.

This brings me to the use of unpooled serum. Kahn[8] reports that only clinically grave cases with toxemia, extreme dyspnea and cyanosis, and extensive lung involvement were chosen, both for serum treatment, and for control. In all, 25 cases received serum; 12 died, giving a mortality of 48 per cent. The control group of 18 similar cases showed 12 deaths, or a mortality of 66.6 per cent.

It is evident from this work that the serum was given the most severe kind of test, yet the difference in percentage of mortality between the treated and untreated cases suggests something more than a mere coincidence. Kahn concludes that from the relative percentage of mortality in the two series, as well as from the surprising beneficial effects of the serum in individual cases, that he believes the serum from convalescent influenza-broncho-pneumonia patients deserves further trial in the treatment of this disease. He does not state whether he used pooled serum. If he did not, the criticism I made concerning the use of serum or blood from single donors holds.

Bass and Ervin[9] at the U. S. Marine Barracks, Paris Island, N. C., selected 55 of the most severely ill patients in their wards. They treated 7 with whole citrated blood and the remaining with unpooled serum. Five out of the 7 receiving the whole blood, and 13 out of the remaining 48 receiving unpooled serum, died; a case mortality of 27 per cent. These writers agree with us that serum from patients without lung involvement is of little value; that donors vary widely in the potency of their sera. They also agree with us in the infrequency of chills, after the use of serum, for only 5 are reported out of the group treated. They conclude that in spite of the high mortality rate, they are satisfied beyond a shadow of a doubt that the use of serum from convalescent influenza-pneumonia patients is of marked value in the treatment of influenza-pneumonia. They emphasize the importance of early diagnosis and treatment.

Finally, I come to the work of Gould[10] at the U. S. Naval Hospital, New York. Gould reports 320 untreated cases of this type of pneumonia, with a death rate of 26.16 per cent., whereas 30 cases treated with unpooled serum showed 2 deaths, or a mortality of 6.6 per cent. I do not mean to infer that this contrast should be accepted as it stands, for Dr. Gould told me that the untreated cases occurred chiefly at the beginning of the epidemic, whereas the cases treated with serum came later. However, I believe it is fair to say that the difference in mortality between the two groups is too great to be accounted for by this time element, especially when I know that many of the treated cases had extensive lung involvement and were decidedly toxic.

Conclusions. After the treatment of over 250 cases of influenza-pneumonia by the use of

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pooled serum from convalescent patients, there remains no doubt in my mind that when a proper diagnosis is made, and the treatment is correctly carried out, both in hospital and private practice, the course of the disease is decidedly shortened, the death rate is at least cut in two, in cases chosen for their severity, and reduced about three-fourths in any large series in hospital practice where the cases are seen early. These conclusions are substantiated by the reports of at least 12 unprejudiced observers.

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DISCUSSION.

DR. FREDERICK T. LORD, Boston:—I have been much interested in Dr. Redden's work. The necessity confronts us of trying to form a judgment whether the method is of value or not. Unfortunately, I do not believe that the question as to its value can at the present time be answered. There are, however, certain considerations which have a bearing on this matter.

There is little to guide us from analogy with other diseases. Ordinary lobar pneumonia is the nearest analogy we have and it may be said that ordinary lobar pneumonia has nothing to do with the kind of pneumonia under discussion. Experimental studies in animals indicate that protective substances are usually but not constantly present in the blood of patients recovering from the disease. Their inconstancy and presence in positive cases only in small amounts do not suggest that a similar method of treatment applied to ordinary lobar pneumonia would be of much assistance.

In attempting to judge the merits of such a method of treatment it is easy to be misled without a control group of cases. The varying mortality from influenza pneumonia without the serum treatment, in this neighborhood, illustrates how cautious we should be. For example, data obtained from Major Paul G. Woolley, Camp Devens, indicate that during the period from October 2nd to October 29th, there were 231 cases of pneumonia at Camp Devens and that of this number 127 (54.9%) died. Of 2,817 cases at Camp Devens from September 4th to October 29th, 787 (27.9%) died. Comparison of Dr. Redden's series with such a group as this would suggest curative value in the serum. But returns from certain other sources indicate that during the epidemic period the mortality from broncho-pneumonia in non-serum treated groups of cases was low. Thus figures obtained from Dr. Marshall H. Bailey of Cambridge in a small number of cases among the Students' Army Training Corps at Harvard show that of 46 cases with the physical signs of broncho-pneumonia and about 15 more with questionable broncho-pneumonia, there were only five deaths, a mortality of 8.1%. No reliable statistics are available for the civilian community; but reports from certain individual physicians practicing in this neighborhood suggest that the mortality from broncho-pneumonia may be even lower than this. Thus one physician reports only one death from broncho-pneumonia and that in a patient with mitral stenosis, among about 25 cases. Another had no deaths in about 15 cases. A third had only one death, and that in a pregnant woman, in about ten cases, and a fourth no deaths in eleven cases. In this civilian group of about 61 cases only two died, a mortality of 3.2%.

We have had too small a group of serum-treated cases at the Massachusetts General Hospital to draw any definite conclusion. We treated 23 cases with the convalescent serum and lost six out of this group. At the same time we had 25 controls and of these we lost only three. There may have been extenuating circumstances among the treated cases, but that is what we have to show and I think that only mortality counts.

DR. EDWIN A. LOCKE, Boston: I have been extremely interested in this work which Dr. Redden and Dr. Maguire have been doing with convalescent serum in cases of influenza with pneumonia, and in private cases have been much impressed with the apparent excellent results of its use. In a small series of fifteen private cases treated during the past fall and winter my experience seemed so favorable that I felt there could be no question of the value of this method of treatment in influenza pneumonia. I must confess also to the same feeling which Dr. Lord has expressed, namely, that if I had the disease I should wish the serum administered. It is difficult, however, to explain the apparent good results on scientific grounds, and personal impressions are not sufficient to prove its value.

Early in February a special service for influenza cases was established at the Boston City Hospital and thus afforded an unusual opportunity to test the effects of the serum from convalescent cases on a series of patients suffering from pneumonia with influenza. In order to

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