ual reduction of diet, as had been, and is now, the routine procedure. This was done in an attempt to discover which method of initial treatment was the more satisfactory from the standpoint of tissue calorie loss. Although the results are not as yet conclusive or fully developed some interesting figures and facts were produced.

Nine cases from the fasting series are here compared with nine cases from the gradual reduction series. No cases of severe acidosis are included in either group. It so happened that each group contains six females and three males. The basis for comparison rests upon two factors, (1) the Harris-Benedict prediction calorie figure, and (2) the acquisition by each patient of tolerance for food furnishing approximately 15 calories per kilogram body weight. That is, the net calorie deficit was calculated daily for each patient until he had acquired a tolerance for food giving him daily approximately 15 calories per kilogram body weight.

TABLE II.

FASTING			GRADUAL REDUCTION		
H. & B.	Total Net Calorie Deficit	Number of Days	H. & B.	Total Net Calorie Deficit	Number of Days
1,151	4,620	6	1,179	3,460	5
1,258	5,041	6	1,022	8,170	13
1,189	5,928	7	1,292	8,670	11
1,397	6,311	9	1,077	8,933	11
1,168	10,003	15	1,182	9,345	9
1,319	14,325	15	1,320	10,449	15
1,274	14,919	19	1,674	10,757	12
1,178	18,150	16	1,480	12,375	19
1,430	30,472	25	1,342	22,100	21
AVER. DAYS		13			14
TOTAL AVER. NET CAL. DEFICIT	12,196			10,473	
DAILY NET DEFICIT	938			748	

938—748=190 calories

The interesting points brought out by this comparison are:

1. The fasting patients averaged only one day less in becoming sugar free and acquiring a tolerance for 15 calories per kilogram body weight.

2. Each day during the experiment, the average patient in the fasting series lost 190 calories more than the average patient in the reduction series.

3. The last patient in the reduction series during the 21 days of treatment lost 22,100 calories,—which is a loss equivalent to 16 days complete fasting, *i.e.*,

$$\frac{\text{Total net calorie deficit}}{\text{Harris-Benedict factor}} = \frac{22{,}100}{1{,}342} = 16+$$

Likewise, the last patient in the fasting series during the 25 days of treatment lost 30,472 calories—which is a loss equivalent to 21 days' complete fasting, *i.e.*,

$$\frac{\text{Total net calorie deficit}}{\text{Harris-Benedict factor}} = \frac{30{,}402}{1{,}430} = 21+$$

No definite conclusions can, of course, be drawn from this small series of cases, but it is hoped that in the future with more comparisons, a definite opinion on the subject will be tenable.

THE USE OF THE SERUM OF CONVALESCENTS IN THE TREATMENT OF INFLUENZA PNEUMONIA: A SUMMARY OF THE RESULTS IN A SERIES OF ONE HUNDRED AND ONE CASES.

BY GEORGE P. SANBORN, M.D., BOSTON.

THIS series of one hundred and one cases of broncho-pneumonia following epidemic influenza was treated with serum of convalescent patients, during the period between December 1, 1918, and May 1, 1919.

The patients referred for serum treatment were distributed for the most part, in the eastern portion of Massachusetts; a few in New Hampshire and Rhode Island, and one in New York.

The diagnosis in all cases in this series was unmistakably broncho-pneumonia, following epidemic influenza, and in a large proportion the diagnosis had been made and confirmed by a consultant before serum therapy was considered. During the same period, I treated by the same method some cases in which the diagnosis of influenza broncho-pneumonia was suspected, but could not be definitely established. These doubtful cases were not included in the series here reported.

Leucocyte counts were made in nearly all cases prior to serum treatment but I now have record of counts in only thirty. Twenty-seven were below twelve thousand, and three were fourteen thousand, seventeen thousand and thirty-four thousand respectively.

Low leucocyte count was the usual finding, and variations above fifteen or twenty thousand were not very common. The occasional high count suggested complicating infection and required sputum examination and typing, if pneumococci were found: but a high count was not taken to contraindicate convalescent serum, because, irrespective of complications,

the important infecting agent was believed to be the same as in the typical cases.

Typing was done whenever a rusty sputum occurred or when the rate of respiration was more rapid early in the pneumonia than would be expected in the typical case. In a considerable number of typings in this series, pneumococci, if found at all, proved to be Type IV.

The importance of typing sputum is shown in a group of cases of probable influenza pneumonia which I treated during the past winter (1919-1920). Type III pneumococcus was found in two cases and Type I in a third. The Type III cases died. The Type I case recovered after three injections of convalescent serum and one of anti-pneumococcus serum.

The majority of the cases of this series were referred for treatment because they were seriously ill and gave the physician concern as to the outcome. The fact that about half of them had been ill from three to seven days when serum treatment was instituted and seventeen died within twenty-four hours, suggests that the serum was put to a severe test.

One hundred fifty-seven doses of serum were administered intravenously to one hundred one patients. The dosage for adults was 100 c.c. and for children 50 c.c. From one to six doses were given each patient according to indications, at eight to twenty-four-hour intervals.

The method of injection was that advocated by Schreiber for intravenous use of salvarsan, using rubber tubing, three-way cock, straight eighteen to twenty-gauge needle and 20 c.c. glass syringe. No discomfort was caused other than that attending the insertion of the needle. In no case was it necessary to cut down on a vein or to inject serum subcutaneously.

The donors of blood, all of them adults, were chiefly private patients, but to some extent were ex-hospital patients who were willing to part with their blood for a consideration.

Those patients only were used as donors who had recovered from an undoubted bronchopneumonia which had followed epidemic influenza. Those giving evidence of having or having had tuberculosis or syphilis were not used as donors. Those who had received convalescent serum as treatment were also made use of and their serum seemed to have satisfactory potency on clinical grounds.

Blood was taken from convalescents as early as three days after the temperature had reached normal and as late as two months after this time. The sera taken during early convalescence seemed more potent than those taken toward the end of the two months' period.

The amount of blood taken at a sitting was from 300 to 500 c.c., and bleeding was repeated once, twice, and occasionally three times at suitable intervals if circumstances would permit. There was never any technical difficulty met in obtaining the desired amount of blood; there was little discomfort occasioned the donor and there were no untoward happenings.

The apparatus used in drawing blood was as follows:

To receive the blood a 500 c.c. wide-mouthed bottle with tight fitting rubber stopper perforated by two glass tubes, one-eighth inch bore, bent at right angles. To one of these tubes or nozzles was connected a thick-walled rubber tube three-thirty-seconds of an inch inside diameter, eight inches long, which had in its free end a male connection carrying a seventeen or eighteen-inch gauge needle of non-corrosive metal. This needle with tube attached, was inserted into a test tube and fixed in place by a tight cotton plug. The other glass nozzle was lightly plugged with cotton. This receiving bottle with needle and tubing attached was wrapped in cloth and sterilized.

To act as a vacuum chamber a second bottle was prepared, similar to the first, but without needle or rubber tubing. When blood was to be drawn the open tube of the sterile receiving bottle was connected by a short rubber tube to one of the glass nozzles of the vacuum bottle and the remaining nozzle of the latter connected by a rubber tube six inches long to the vacuum pump.

Technique. The donor assumed a recumbent position with arm outstretched and resting on a table or chair. The apparatus as shown in Fig-

FIGURE 1.—Apparatus for obtaining blood as used at the Boston City Hospital.

ure 1 was placed in a convenient position close to the arm. After carefully sterilizing the skin at the flexure of the elbow a tourniquet was applied with proper tension. The rubber tube with needle attached was removed from the test tube and the needle inserted into a prominent vein. If properly located within the lumen, blood flowed at once into the bottle. The flow was accelerated by means of the vacuum pump so that clotting in the needle was prevented.

A sufficient amount of blood having been obtained, it was allowed to clot in the bottle at room temperature for several hours. The clot was then separated from the wall of the bottle by shaking, and the bottle placed in the ice chest over night.

The following day serum was pipetted off, centrifugalized to remove red cells, bottled, labelled with the donor's name, and a specimen of the serum taken for the Wassermann test. When serum was urgently needed, the procedure could be cut short and the available serum prepared in from four to six hours.

Serum was pooled as it was required for treatment of a given case. For each 100 c.c. dose, equal parts of as many individual sera as were on hand, were used. Pools usually contained serum from three to five different donors. It was not the rule to add preservative to the serum because it was kept at a low temperature and was used within a day or two and often within a few hours of its preparation. To those sera which were kept more than two or three days, three-tenths of one per cent. of chloroform was added.

The potency of pooled serum seemed to be fairly constant, judged by its apparent clinical effect among cases treated early in the pneumonia.

Of the sixty-seven cases that recovered, fifty-nine required one or two doses; seven, three; and one, six. The maximum dosage of serum in a given case in the recovered group was 700 c.c.

Of thirty-four cases that died, seventeen that received one dose did not live a sufficient length of time to receive a second. The remaining seventeen received two to four doses and two of them received 500 c.c. and 700 c.c., respectively, as the total dosage.

Reactions following serum were conspicuous by their absence. There were no cutaneous eruptions and there was nothing suggestive of anaphylaxis. In not more than ten per cent. of the cases there occurred a chill which was usually slight, not prolonged and not at all prostrating. Chills did not occur after subsequent doses in a given case. Not more than two or three patients complained of serious discomfort accompanying the chill. Nothing occurred in the way of a reaction that could possibly lessen the chances of recovery even in the case of the sickest patient.

About one-half of the cases were seen a second time and this only because more treatment was called for. Through the kindness of the attending physicians I have charts of a fair proportion of the cases and information as to the end results in all of them.

The course of the temperature after injection of convalescent serum is of some interest. Among the recovered cases forty-three received but one dose of serum. Of these I have record of twelve and in eight of these temperature fell to normal within twenty-four hours; in two it fell in thirty-six hours and in two in forty-eight hours. Of sixteen cases receiving two doses I have record of three. One fell to normal in thirty-six hours; one in forty-eight and one in one hundred and twenty hours. Of seven cases receiving three doses each, one temperature came down in forty-eight hours and two in sixty hours.

One case received four doses and is worthy of special note. The temperature dropped gradually during ninety-six hours, condition improved but delirium continued. He was transferred to the McLean Hospital where about a month later he developed a second bronchopneumonia and again became critically ill. Two more injections were given on successive days, temperature fell to normal in forty-eight hours and he recovered.

Among thirty-four cases that died, seventeen died before a second dose of serum could be given. In these seventeen cases no constant effect was noted, either favorable or unfavorable, that could be ascribed to the serum. Among ten who lived to receive two doses, there was a drop in temperature in four, but general condition was not evidently affected. In five cases no change was noted.

One of the cases receiving two doses is of interest because he died several days after his temperature had reached normal and convalescence appeared established. He suddenly developed oedema of the lungs and died in a few hours.

Five cases received three doses; three died in forty-eight hours and there are no records of the other two.

Two received four doses. In one the temperature gradually fell to normal on the fourth day. In spite of this, respiration and pulse remained high and the patient died having had a normal temperature for four days. In a second case treatment was begun on the second day of the pneumonia and 700 c.c of serum was administered within about forty-eight hours with no effect. Hemolytic streptococcus was found predominating in the sputum.

Beginning between twelve and twenty-four hours after the serum injection among those who recovered, there usually developed a consistent and unmistakable improvement; cyanosis became less marked, toxic symptoms were relieved and a sense of well being appeared gradually to be established. The change from a sick to a convalescent patient seemed to me very clean cut, more so than in the usual non-serum treated case that I have seen, and reminded me somewhat of the effect of diphtheria antitoxin when given in sufficient amount to an appropriate case.

There were practically no complications in recovered cases. One case already described did not recover from his delirium for some weeks and developed a second attack of broncho-pneumonia from which he recovered. A second case developed a Type IV lobar pneumonia after the temperature had been normal about twenty-four hours, but recovered. The percentage of complications was three.

There were nine cases of pregnancy in this series, and two deaths, both following miscarriage. The percentage of mortality was twenty-eight. The reported mortality among pregnant women was high.[7, 8] In one series thirty-four per cent. died and pregnancy was interrupted in thirty-seven per cent. of all cases; in a second group, fifty per cent. mortality; in a third, the mortality when pregnancy was interrupted was eighty per cent. and when uninterrupted, forty-eight per cent. Other groups have been reported with lower mortality rate.

The mortality rate in this series of one hundred one serum treated cases was thirty-three and six-tenths per cent. In one hundred eighty-four cases of influenza-pneumonia not treated by serum, occurring in the practices of six different physicians in this vicinity, during the same period in which this series was treated with serum, the mortality was twenty-one per cent.

TABLE I.

MORTALITY RATES OF INFLUENZA-PNEUMONIA IN THIS VICINITY TREATED IN PRIVATE PRACTICE WITHOUT SERUM, DURING THE PERIOD DECEMBER, 1918, TO MAY, 1919.

PHYSICIAN	NUMBER OF CASES	DIED	MORTALITY PER CENT.
W. C. M.	7	1	14
M. E. C.	16	4	25
M. C. A.	20	5	25
W. E. F.	35	9	25.3
F. R. S.	19	1	5.2
T. J. O'B.	87	19	22
TOTALS	184	39	21

Using this untreated group as controls, it will be seen that the serum treated group has a higher mortality rate by twelve per cent.

The factors contributing to this high mortality rate in the treated cases, as compared with the controls, were several. The serum treated group was composed largely of cases selected for special treatment because they were severe, while the control series were the average cases as they occur in private practice. Seventeen of the thirty-four cases that died were practically moribund when seen and died within twenty-four hours after the serum was given; two died of an early developing complication due to the hemolytic streptococcus; two others died some time after the temperature had reached normal, associated with sudden developing pulmonary oedema. The most important factor which perhaps makes unnecessary the mention of the above is that twenty-eight of the thirty-four who died did not receive serum until after the pneumonia had been under way three to eight days. Influenza pneumonia is extremely rapid in its progress. The average period of life in one group of thirty-nine fatal cases, was four and seven-tenths days.[13]

It is reasonable to suggest, on this basis, that the period during which influenza pneumonia is most amenable to any therapeutic method, does not extend much beyond the first four or five days of the disease, and to assume that the above noted twenty-eight cases first treated by serum on or after the fourth day, did not have a safe margin of time for a serum to bring a broncho-pneumonia to a standstill and to start its reversal. These twenty-eight cases determined the high mortality rate for this series, as is shown in Table II.

The generalization that an antiserum is ef-

ficient according as it is given early in a disease and becomes less and less efficient as its administration is delayed from day to day, seems generally accepted. In diphtheria, when serum is administered on the first day of the disease, the mortality should be and generally is, nothing; given on the sixth day, the mortality is nearly three times that on the second.[14] In lobar pneumonia, Type I serum is efficient during the first six or seven days of the disease, and the earlier in this period it is given the more certain the favorable outcome. After this period it rapidly loses its curative value. It is permissible, therefore, to judge the value of an antiserum upon the results among cases treated early in a disease contrasted with the results among those treated first during the later stages.

Table II was prepared to show the mortality rate in this series of one hundred and one cases according to the day of the pneumonia upon which the treatment was begun. No cases are excluded from this table.

TABLE II.

MORTALITY ACCORDING TO THE DAY OF PNEUMONIA UPON WHICH CONVALESCENT SERUM TREATMENT WAS INSTITUTED.

DAY OF PNEUMONIA	NO. OF CASES TREATED	RECOVERED	DIED	PER CENT. MORTALITY
2nd	20	18	2	10%
3rd	35	31	4	11%
4th	17	11	6	35%
5th	15	4	11	73%
6th	9	3	6	66%
7th	3	0	3	100%
8th	2	0	2	100%
TOTALS ...	101	67	34	33.6%

As shown in the above table, twenty cases received the first serum injection on the second day of the pneumonia, and ninety per cent. recovered: thirty-five received it on the third day and eighty-nine per cent. recovered: of seventeen treated on the fourth day, sixty-five per cent. recovered: of fifteen on the fifth day, twenty-six per cent. recovered, while of the five cases treated on the seventh and the eighth days, none recovered.

Serum treatment instituted on the second or third day of the pneumonia resulted in mortality of ten and eleven per cent., respectively; instituted on the fourth day, the mortality was three times that on the third; on the fifth day the mortality was seven times that of the second or third day.

The number of cases for each day from the fifth to the eighth was comparatively few, but all cases combined, it amounted to twenty-nine cases with twenty-two deaths and a mortality rate of seventy-five per cent. There were seventy-two cases treated during the first four days of the pneumonia with a mortality rate of sixteen per cent. Thus the mortality rate among the cases treated the last four days of this eight-day period was more than four times the mortality rate among those in which treatment was instituted during the first four days.

In fifty-five cases serum treated on the second and third day of the pneumonia the mortality rate was ten and one-half per cent. The mortality rate of the one hundred eighty-four control cases treated in private practice without serum was twenty-one per cent., or exactly twice as great as that of fifty-five cases treated by serum on the second and third day of the disease.

Analysis of the statistics in this group of cases indicates that the mortality rate increased according as administration of serum was deferred from day to day and suggests that convalescent serum may have had curative value during the first few days of the pneumonia; that its efficiency from then on became rapidly less in proportion as the condition of the patient seen later and later in the disease became more and more serious and rendered him less amenable to treatment of any kind.

MacLachlan and Fetter's series of forty-seven cases was treated by citrated blood, and the mortality rate indicated according to the day upon which treatment was instituted. It was ten per cent. in cases treated on the first day of the pneumonia, twenty per cent. for the third day, and fifty-seven per cent. when treatment was delayed until the fourth day. The curve of increase of mortality rate is broken on the second day by a rise to forty per cent.; the total number of cases is few, particularly on the third and fourth day, and seven cases that died within twelve hours were omitted from the statistics. Nevertheless the difference in the mortality rate of the cases treated early and those treated later is in general consistent with the differences in mortality rate between the cases treated early and those treated late in the disease in the series here reported.

In one hundred fifty-one cases at the Naval Hospital, Chelsea, reported by McGuire and Redden,[2] convalescent serum was administered during the first two and one-half days of the disease (average) and the mortality rate was

four per cent.; whereas in Dr. Redden's series of one hundred cases in private practice,[3] treated on the average two to five days later in the pneumonia, the mortality rate was sixteen per cent. or four times that of the early treated group at the Naval Hospital. Thus is suggested the possibilities of serum treatment instituted in the very early stages of pneumonia, as compared to the later stages.

Opinions as to the value of convalescent serum, citrated plasma, or citrated whole blood, in relation to their early administration, are expressed in a number of published articles on the treatment of influenza pneumonia by blood or blood fluids of convalescent cases. They are as follows:

Hartmann and O'Malley:[5] Serum must be given early if a large percentage of recoveries is to be expected.

MacLachlan and Fetter:[4] Citrated blood of convalescent pneumonias has beneficial effect if given early. Beyond the third day it is of little value.

Stoll:[12] Occasionally of value when used as late as the fifth day. Used on the first three days, it seems to lower the mortality rate and to diminish complications.

Bass and Ervin:[10] Of marked value, but early administration important.

Redden:[3] Course of disease shortened. Death rate cut in two in cases chosen for their severity. Death rate reduced three-fourths in large series in hospital practice where cases are seen early.

This expression of opinion based on four hundred and fifty-five treated cases, briefly stated, amounts to this; convalescent serum is of value in proportion as it is given early in pneumonia. This is consistent with the expectations in the case of antisera of established value, and with the finding in the series of cases reported in this paper, based on the mortality rates calculated according to the day of pneumonia on which treatment was initiated, namely, that the time factor, that is the period between the onset and the day of treatment, had a very close relation to the mortality rate, and largely determined the success or failure of convalescent serum.

A correct estimate of the value of convalescent serum is impossible if based on the total mortality rates now available, not only because they vary so widely in different treated groups of cases, but also and chiefly, because there are no stable mortality rates in untreated cases for comparison. No matter how low a mortality rate is achieved (unless it be zero) in a given group of treated cases, a group untreated, with as low a rate is apt to be found.

The statistics of the controlled groups of Hartmann and O'Malley, Ross and Hund, Kahn,[9] Gould,[11] the uncontrolled groups of McGuire and Redden, and the series reported in this paper, would seem to justify a favorable estimate of the value of convalescent serum.

On the other hand, in the carefully controlled series of Locke[15] (twenty-two cases, twenty-two controls) and Lord[16] (twenty-two cases, twenty-five controls), the treated cases have a mortality rate in the one case as great as, in the second greater than that of the controls.

The mortality rates based on the day treatment was begun, in the series reported in this paper, showed that the period of the disease before treatment was instituted had a direct bearing upon the outcome of the case. Consequently correct judgment of value or lack of value of serum in a given group of cases, requires data as to the day of the disease on which serum treatment was instituted in each case. For it cannot be questioned that two groups, one treated and one untreated, seen first late in the disease, would not only have a high mortality rate, but that rate would be about the same for both groups. A small group, even of controlled cases, therefore, is apt to lead one astray, particularly in hospitals where late and serious cases are apt to predominate. A very large series of controlled cases is necessary, particularly in hospital practice, in order to equalize the effect of the severe cases upon the mortality rate.

CONCLUSIONS.

Convalescent serum proved a safe therapeutic agent.

Clinical improvement consistently followed its administration in cases that recovered and in some that died, and gave the impression that it had therapeutic efficiency.

The total mortality rate for this series was not a measure of the value of convalescent serum, but was an index of the severity of the disease in the group as a whole.

Mortality rates calculated according to the day on which serum treatment was instituted in each case, as in Table II, furnished the es-

sentials for an approximate estimate of the value of convalescent serum in this series of cases.

Convalescent serum appeared to have value when it was administered during the first three days of the pneumonia, in this series of cases. This conclusion is based on a mortality rate of ten and one-half per cent. as against twenty-one per cent. in a control series of one hundred eighty-four cases of average severity, occurring in private practice at the same period of the year, in the same general locality, but not treated by serum.

Its value rapidly decreased when administered after the third day of the pneumonia as indicated by rapidly increasing mortality rates, according as administration was delayed from day to day. Given during the first three days, it was three times as efficient as when delayed until the fourth day, and seven times as efficient as it was when deferred until the fifth day. Given during the first four days of the pneumonia it was five times as efficient as it was when given during the succeeding four days.

The time factor, that is the period between onset and day of treatment, had a close relation to the mortality rate and seemed largely to determine success or failure. This corresponds to findings in case of sera of established value.

Total mortality statistics of uncontrolled as well as of small controlled series, because of the obvious effect of cases treated late in the disease upon total mortality rates, are of little value as basis for an accurate estimate of the efficiency of convalescent serum.

Complicating infection by hemolytic streptococci accounted for two deaths in this series. Although the antibody content of convalescent serum is uncertain in character and concentration, the serum undoubtedly would not regularly contain antibodies to the type pneumococci or to the streptococci, which would be specific for the case treated. Since a number of such cases may occur in any series of influenza pneumonia cases, the effect upon the mortality rate would have to be considered.

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DISCUSSION.

DR. LESLEY H. SPOONER, Boston: My experience in the treatment of influenza pneumonia, which Dr. Sanborn has taken up so exhaustively, has not been sufficient to warrant any authoritative addition to the discussion. I wish to express, however, my personal appreciation for Dr. Sanborn's work and for his presentation of the matter.

I feel that it would not be amiss to call your attention to a phase of serum therapy which has been too much neglected, but which ranks only slightly less in importance than the specific treatment of pneumonia of both influenza and lobar types.

During the influenza epidemic at Camp Devens, September and October, 1918, except for the acute fulminative pneumonia—which was classified by pathology and bacteriology as influenzal—a large percentage of fixed types of pneumococci was found in the sputum of those individuals showing signs of pneumonic complications. This observation was corroborated by limited work upon blood cultures, made from blood of the same patients.

From a clinical standpoint it is of especial interest to note that the pneumonia in these individuals was almost entirely of the bronchial type.

Although Cole and others have demonstrated the absolute indication for treating with specific serum the cases of acute lobar pneumonia, presenting Type I organisms, not enough stress has been laid upon the application of this therapy to corresponding cases of bronchopneumonia.

Our work shows that at that period the mortality of all types of pneumococcus infection was at least doubled. As a result evidently of specific therapy the mortality in fifteen cases was reduced to seven per cent.

This compares very favorably with observations of other investigators, since the same mor-