SPECIAL MINNESOTA STATE MEDICAL ASSOCIATION MEETING NUMBER

Staff Meeting Bulletin Hospitals of the » » » University of Minnesota

Human Serum and Plasma Therapy

Volume X | Friday, June 2, 1939 | Number 30

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

Volume X | Friday, June 2, 1939 | Number 30

INDEX

Published for the General Staff Meeting each week during the school year, October to May, inclusive.

Financed by the Citizens Aid Society.

William A. O'Brien, M.D.

I. LAST WEEK

Date: May 26, 1939

Place: Recreation Room,
Powell Hall

Time: 12:15 to 1:15

Program: Movie: "Donald's Nephews"

Artificial Fever Therapy
Ultra Violet Radiation Therapy
M. M. Cook

Discussion
Wesley W. Spink
K. W. Stenstrom
E. Klaveness
Arild E. Hansen
M. M. Cook

Present: 104

Gertrude Gunn
Record Librarian

II. MOVIE

Title: "Human Convalescent Serum"

Released by: Los Angeles Convalescent Serum Center.

III. ANNOUNCEMENTS

HUMAN SERUM LABORATORY

Although funds were available at the beginning of the present school year for the establishment of a human serum laboratory it was nearly the middle of the year before the preparations met with the approval of those in charge and the unit was opened. Located in the department of Pediatrics on the second floor in the out-patient department, it is within easy access of both in-and out-patient services. Everything in the unit has been purchased or built for a specific purpose. The staff consists of Paul F. Dwan, Clinical Instructor of Pediatrics, Erling S. Platou, Clinical Associate Professor of Pediatrics, Evelyn Johnson, Head Technologist and Mary P. Slattery, Laboratory Assistant. Drs. Dwan and Platou have long been interested in the use of human serum in the prevention and treatment of disease thru their work in the contagious disease service. It was natural for them to be at the Philadelphia meeting three years ago when the Human Serum Association was formed and at San Francisco the next year at the second meeting. In the interval they had gone around the country (one to the east, the other to the west) in order to inspect serum laboratories and meet physicians interested in this activity. When Evelyn Johnson (M.D. University of Minnesota 1935) joined the staff, she went on another tour of laboratories in Milwaukee, Chicago, and New York, spending some time in each in order to become better acquainted with the technical details. This tour lasted two months. Mary Slattery, student in Bacteriology had previously been connected with the Chicago Serum Laboratory and as Minneapolis was her home, she did not find it difficult to return here. The purpose of the laboratory is both investigation and service. At the present time blood is being collected from recently recovered patients who have had measles, scarlet fever, and mumps. In addition medical students are being immunized with pertussis antigen and their blood is being collected. Convalescent patients are used from one week to 3 months after recovery. They are paid for their blood and the blood serum is sold at a moderate price in order to help support the unit (this is standard practice elsewhere). It is interesting to note the price of measles serum is $2.50, the same as globulin. Other sera are $5.00 for 20 cc. (prevention) or $25.00 for 100 cc. for treatment (scarlet fever). Technical details are interesting as the serum is checked three times for sterility. It is also checked for syphilis, titre and passed through the Berkfeld filter. Investigations of the use of serum and plasma are in progress (poliomyelitis and protein deficiencies). The Center met the test of a measles epidemic in the first six months of operation (with great success). The services of the Serum Laboratory are available to all physicians. This special issue of 2500 copies of the Bulletin is to acquaint everyone with the work of the Human Serum Laboratory. The Serum Laboratory was made possible by a gift from Mrs. Helen R. Dwan.

IV. HUMAN SERUM AND PLASMA IN THE PROPHYLAXIS AND TREATMENT OF DISEASE

Erling S. Platou
Paul F. Dwan
Evelyn Johnson

The merit of human blood in treating various diseased conditions of the body is clinically well established. However, specific effects of some component parts of the blood which are not well understood are more than ever becoming the interest of investigators. This review deals particularly with the use of convalescent human serum in the prophylaxis and treatment of some of the acute infectious diseases. The use of dessicated and concentrated human serum and plasma in infections and physiologically altered states is also considered.

Sporadic attempts at immunization by inoculations with blood were made as far back as 1780 (Stoll[1]). These were directed against a variety of diseases, but perhaps the first disease in which convalescent blood was used adequately was scarlet fever.

SCARLET FEVER

Since scarlet fever convalescent serum represents the first, and perhaps the most effective, therapeutic application of any human serum it assumes a position of particular interest in this discussion. The well-known fact that scarlet fever usually produces a lasting immunity prompted its use by Weisbecker[2] as early as 1897.

Transfer of syphilis and the lack of availability of processed serum served as deterrents to the early use of scarlet fever convalescent serum. Following the advent of the Wasserman test, however, numerous reports on its efficacy in therapy appeared, noteworthy among which have been those of Reiss and Jungman[3], Rowe[4], Koch[5], Zingher[6,7], Weaver[8], Schultz[9], Kling and Widfelt[10], Gordon, Bernbaum, and Sheffield[11], Johan[12], and Hoyne, Thalhimer, and Levinson[13]. All observers agree that scarlet fever convalescent serum is clinically effective; most feel that its early administration in large doses intravenously to quickly combat the rapidly appearing toxemia of scarlet fever is usually followed by dramatic improvement. Although some physicians recommend immunotransfusion for this purpose, it is felt by the majority of those reporting that pooled human serum from variable sources is more effective (and more readily available since the establishment of human serum laboratories).

Dick and Dick[14], although admitting the presence of antitoxin in human serum, feel that commercially prepared horse serum with a high antitoxic titre is immunologically superior to human serum. Rhoads and Gasul[15] have shown by titration methods that twelve representative lots of convalescent serum contained an average antitoxic potency of only 500 neutralizing units of antitoxin per cubic centimeter as compared to 150,000 units per cubic centimeter in commercial antitoxin (about 1/30 as strong in antitoxic units).

In spite of this relatively low antitoxic titre of convalescent serum, the clinical results reported by Thalhimer, Hoyne, and Levinson[13] following therapeutic doses of 40 cc. compared favorably with those reported by one of us[16] at about the same time, following the use of commercial antitoxin in doses fifteen times as large when expressed in antitoxin neutralizing units.

These two groups of cases listed in tables one and two contain about the same percentage of severe types and were observed at same time in nearby midwestern cities although they are not identical samples. The roughly similar reduction of principal complications in the two series as compared to controls suggests the possibility that factors other than antitoxic titre may explain the results obtained with human convalescent serum.

Table I

Principal Complications in Cases Treated with Human Convalescent Serum as Compared to Controls

983 Treated Cases		6,282 Controls
9.5%	Lymphadenitis	27.0%
8.8%	Purulent Otitis Media	13.6%
0.2%	Hemorrhagic Nephritis	3.6%
18.5%	Total	44.2%

Table 2

Principal Complications in Cases Treated with Commercial Antitoxin as Compared to Controls

1,664 Treated Cases		2,000 Controls
3.9%	Lymphadenitis	11.7%
5.9%	Purulent Otitis Media	12.7%
0.8%	Hemorrhagic Nephritis	3.8%
10.6%	Total	28.2%

Although massive doses of convalescent serum are required to match the antitoxic titre of commercial antitoxin, it is believed by some that such quantities of human serum are clinically much more effective than an equivalent amount of commercial antitoxin. This is offered as further evidence that convalescent serum is to some extent antibacterial, or at least that its beneficial effect is not limited to its specific antitoxic content. Our own experience with massive doses of convalescent serum in critically ill patients suggests that this is true. Several workers have found increased bactericidal power against hemolytic streptococci in serum obtained from patients with various diseases associated with these organisms. For example, Hare[17] detected in the sera of patients who recovered from puerperal fever an augmented bactericidal action against hemolytic streptococci isolated from these patients. Fothergill and Lium[18] also used homologous organisms and demonstrated an increased activity in the sera of two patients who recovered from scarlet fever accompanied by complications, but in two other scarlet fever patients without complications no increased bactericidal power was noted. Using another method of approach, Tunnicliff[19] observed that 26 different lots of pooled sera from scarlet fever patients possessed a high opsonic index to "Streptococcus scarlatinae." Hare found that patients suffering from puerperal fever due to the hemolytic streptococcus possessed in their serum a heat stable opsonin against the homologous organism.

We are privileged to quote from a personal communication from Dr. Elizabeth Moore and Dr. William Thalhimer[20] who have recently completed a study of some of the immunological properties of scarlet fever convalescent serum. In their study they have determined the antitoxin content and bactericidal power of convalescent scarlatinal sera which are pooled and distributed by the Manhattan Convalescent Serum Laboratory for the prophylaxis and treatment of scarlet fever.

"Observations on the streptococcus antitoxin content of 51 sera from patients convalescent from scarlet fever indicate that this antibody is generally present in amounts of less than 10 units per cu-

bic centimeter (U. S. Standard) which is in agreement with the findings of others. Rhoads apparently assumed that the beneficial therapeutic effects of convalescent serum were dependent solely upon the antitoxin content of the serum, and as a result believed that serum is rarely given in adequate dosage. It is not the purpose of this communication to enter into a clinical discussion of dosage, but rather to point out that immune substances other than antitoxin are present in convalescent in demonstrable amounts and may contribute to the effectiveness of the serum.

"The present observations indicate that bactericidal substances which appear in the sera of patients after an attack of scarlet fever are type-specific in their action on virulent hemolytic streptococci. Seventy-four per cent of 34 sera acted upon one of three virulent types of streptococcus employed, but no serum had an effect on more than one of these types. On the other hand, eight of the 20 sera (40%) which reacted with the avirulent NY5 strain were also active against one of the three virulent strains. Evidence is insufficient to offer an explanation for the greater incidence of bactericidins against the NY5 strain, or for the relative lack of type-specificity displayed by these substances. It should be borne in mind, that this strain, apparently because of its lack of M substance, gives many cross as well as certain type-specific reactions.

"It has been the custom to pool lots of serum obtained from 30 to 40 patients who have recently recovered from scarlet fever before dispensing convalescent serum for clinical use. This empirical procedure, which has given successful clinical results, now has experimental evidence to warrant its continuation. Since several types of hemolytic streptococci are encountered in each epidemic, the chance of including the proper type-specific antibodies for the less frequently occurring organisms is small unless a number of sera for each type are present in the pool. On the other hand, it is probable that a pool made up of sera collected from patients in a given epidemic will contain many antibodies against the types of hemolytic streptococci most commonly encountered in that epidemic. For this reason it is important that convalescent sera be collected early in the epidemic, pooled, and used for therapeutic purposes while the organisms against which the antibodies have been elaborated are still predominant. All of these difficulties would be obviated were it the general practice in hospitals to type the streptococcus responsible for the infection just as is done in the diagnosis and treatment of pneumonia due to the pneumococcus. Antisera for each type of streptococcus could be pooled and used for the treatment of patients with infections caused by the corresponding type of organism. Lyon has suggested a somewhat similar procedure in treating patients with hemolytic streptococcal infections other than scarlet fever by transfusion from donors with a high specific antibacterial immunity as determined by the opsonin method.

"It is of considerable importance to know how long anti-streptococcal immune substances persist in the blood of patients after infections, and how well these substances withstand storage, for a serum laboratory must obtain large amounts of convalescent blood and must maintain a considerable reserve stock. Observations indicate that both antitoxic and bactericidal substances against hemolytic streptococci generally persist in patients' serum for at least six months after onset of scarlet fever and these properties of serum are not lost after storage in the cold for considerable periods. The persistence of bactericidal substances in the sera of patients with scarlatina, as well as their relative specificity, would appear to differentiate them from the non-specific bactericidal agents present during acute infections."

Any discussion of the treatment of a hemolytic streptococcal infection would seem incomplete without reference to the use of sulfanilamide. During 1937-38, 100 patients were treated at the Minneapolis General Hospital[16] while 100 were observed as controls. While only eight complications occurred among the treated and 41 complications occurred in the con-

trols it was strikingly observed that the treated cases were equally toxic during the acute phase of the disease. It would seem, therefore, that as in some other diseases sulfanilamide acts indirectly through specific antibodies which have either been actively produced or passively transferred. Patients who received specific antibodies manifested a prompt reduction in toxic features.

The most dramatic results in our experience treating scarlet fever to date have been with the combined use of convalescent serum and sulfanilamide.

Although many reports on the use of serum alone for prophylaxis have appeared, we have witnessed some failures with the small doses usually employed for this purpose. To date, although our experience has been limited we have experienced no failures even with intimate exposure following the combined prophylactic use of 20 cc. of scarlet fever convalescent serum and sulfanilamide.

SERUM TRANSFUSIONS FOR SEPTICEMIA

A favorite form of treatment used by many physicians in cases of septicemia is the administration of transfused blood. The transfusion is generally not given because the patient needs the blood, but because he needs the immune substances contained in the transfused blood. It has been observed many times that patients with septicemia show a slight increase in the complement titre of their blood at the onset of the illness. The amount of complement decreases as the infection progresses and with recovery gradually returns to normal. In severe cases, the complement continues to decrease and many severely ill patients show a complete absence of complement. Most of the patients dying of septicemia show a great decrease or a total absence of complement in their blood. It would therefore seem that complement contributes a very important immunological factor in combatting infection.

It has been shown by Cadham[21] and others that patients transfused with large or moderate amounts of whole blood suffer a severe loss of complement. When serum alone is administered not only does this loss not follow but complement actually increases. From this it may be assumed that the decrease in complement which follows whole blood transfusion is due to the cellular portion of the blood. Moreover, it has been shown that transfused serum actually stimulates the production of complement in the patient. Complement titres taken following transfusions with serum become higher than could be accounted for by the complement contained in the transfused serum, so we must infer that the added amount is produced by the patient himself, due to the stimulating action of the complement contained in the transfused serum.

MEASLES

Reports on the use of convalescent measles serum have contributed to a vast medical literature. Most reports are impressions formed from small groups of uncontrolled cases. It was not until effort was made to collect, pool, and preserve a large supply of serum that reports of controlled experiments began to appear in the medical literature. However, many of these observations will bear repeating.

Although the credit for the therapeutic use of measles serum belongs to Weisbecker[22], Cenci[23] was apparently the first one to attempt to passively immunize children against measles in 1901.

Degkwitz[24] in 1922 observed that more than 90% of children over eight months old are susceptible to measles. The prodromal stage of measles being so highly infectious, he points out that by the time the diagnosis is made, all the children who have been in contact with the patient may have been infected. No case of untoward effects of inoculation was observed by him in his series of 1700 cases. With the exception of two or three per cent failures his results were uniformly good. He stated that the duration of passive immunity gained was uncertain and varied from 33 days to a year.

Debré, Bonnet and Broca[25] (1925)

demonstrated a peculiar phenomenon, namely, inhibition of the measles rash at the site where convalescent serum had been previously injected.

Nicolle and Conseil[26] (1923) recommended that samples of serum be pooled, thus assuring uniform antibody content. They employed a method of sero-vaccination, which consisted in the injection of 10 cc. of convalescent serum and 24 hours later, of one cc. of the blood of a measles patient in the acute stage of the disease. They felt that this method was harmless, and that the immunity conferred was probably more lasting than that conferred by the injection of convalescent serum alone.

Buttenweiser[27] (1924) published several tables illustrating the importance of measles as a remote or immediate cause of death among infants contracting measles in a hospital. He stated that one-sixth of all deaths in the hospital were due to measles contracted during their stay. He recommended the prophylactic injection of convalescent serum in all babies exposed.

Regan[28] (1924) recommended late immunization of susceptibles so that the course of the disease becomes attenuated, thereby producing an active immunization as well as a passive immunity. This procedure has now become adopted for older healthy children. He recommended injections between the sixth and ninth day of incubation in doses of from eight to ten cc.

Park[29] published his successful results with convalescent measles serum in 1924. He reported over 1500 children who received preventive injections.

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The following table shows his results:

Amount of Plasma Injected	Number of Children	Modified Measles	Unmodified Measles	Complete Success
3 cc.	219	20%	8%	72%
4 and 5 cc.	190	8%	2%	90%
6 to 10 cc.	243	6%	2%	92%
Total in Institutions	753	11%	5%	84%
Total in Families	226	42%	5%	52%

Copeman[30] (1926) described a technique for the standardization of measles convalescent serum. By making use of the phenomenon described by Debre' (inhibition of the rash at the site of previous serum injections) he sought to standardize sera. He did this by injecting several sera in the preeruptive state and observing the degree of inhibition of the rash.

Kato[31] in 1928 gave a statistical summary as to the number of immunizations reported in the literature, which revealed that 10,000 persons have thus far been passively immunized. Nine thousand of these were successful and the majority of the remainder had the disease greatly modified.

The mortality rate from measles can reach appalling proportions when epidemics break out among poorly nourished or debilitated children. The Lancet[32] in 1930 recorded a severe epidemic among German peasants who were emigrating from Soviet Russia to Canada. The disease affected 192 children and caused 52 deaths. The scourge was finally stopped by the use of convalescent serum.

Marie[33, 34] (1922) and DeCastro[35] (1922) introduced dried serum which was put up in ampoules. They felt that the serum would retain its antibody content indefinitely. This is generally accepted today and has enabled laboratories to build up a reserve of serum during a measles epidemic. When needed, this dried serum is then re-dissolved in ster-

ile distilled water to the desired concentration.

Thalhimer[36] stresses the need for serum in all children under five, for all debilitated children and for use in institutions to prevent epidemics. He advised reinoculation when measles is prevalent as a beneficial and inocuous procedure.

Convalescent measles serum is potent when obtained as early as the tenth day after the beginning of the illness, provided the patient has been fever free for at least seven days. It is similarly potent when obtained as long as four months after recovery, and perhaps longer. The determination of how long a recovered individual will yield efficacious serum needs more accurate determination.

The dosage of serum necessary for prophylaxis varies, but is usually stated as follows:

Infants and children under 3 years	5 cc.
Children over three years	7.5 cc.
Adults	10-15 cc.

Levinson and Conner[37] studied the therapeutic effect of serum on a group of 16 children. The cases studied were patients at the Municipal Contagious Disease Hospital in Chicago, who were in the hospital because of some other infectious disease. They developed measles either from an inadvertant exposure, in the hospital, or from a previous unsuspected exposure before admission. In the 16 cases studied in this way, six patients received 20 cc. of serum; four, 30-40 cc.; and six, 50 cc. This was given intravenously in the preeruptive stage. The cases were studied from the viewpoint of the temperature, the character of the exanthem, and the severity of the invasive symptoms. It was found that the temperature curve dropped to normal and failed to rise with the appearance of the rash as would be expected with an untreated case of measles.

The exanthem was attenuated and altered in appearance and the Debre' phenomenon was noted. The most marked effect was noted in the symptomatic response. This alleviation of symptoms was striking in view of the past experience with measles developing in sick children in the hospital.

They conclude that the serum in large doses was of definite value but because of the massive doses that are required, it is obvious that treatment of measles will necessarily have to be limited to selected cases. Whereas the prophylaxis of measles may be practised generally because of the small dose required for prevention, treatment will have to be limited to those children in whom the development of measles would offer a grave prognosis.

PERTUSSIS

The evaluation of the use of convalescent serum in pertussis is a very difficult matter. Because of the duration of the incubation period and the extreme variability of the disease, the results are hard to interpret. However, the seriousness of the disease in infancy and the fact that whooping cough and its complications causes so many deaths under the age of two, makes it necessary that we do what we can. Meader[38] reviewing the board of health statistics of Detroit from 1920-1927 found the following mortality per 100 cases reported:

Year	Cases Reported	Deaths Per 100
1920	2,790	4.9
1921	2,691	4.0
1922	2,469	3.6
1923	2,745	3.0
1924	2,062	2.8
1925	3,305	2.6
1926	3,041	2.9
1927	3,646	1.7

Since 1928 convalescent serum has been used in the prevention and attenuation of pertussis in Detroit. Considering the large number of cases involved, perhaps the lowering of the death rate from pertussis before and after serum introduction may be valuable.

The statistics for the ten year period from 1928 through 1937 follow:

Year	Cases Reported	Deaths Per 100
1928	5,395	1.6
1929	4,100	2.2
1930	3,467	1.3
1931	5,389	1.2
1932	5,922	1.3
1933	4,986	0.9
1934	4,304	0.7
1935	5,587	0.8
1936	7,433	0.6
1937	3,352	0.7

This type of analysis gives us some basis for conclusion as to the merit of a given form of treatment, but of course is not a controlled experiment. Meader followed 183 children exposed to whooping cough and found that 121, or 66% of them developed the disease. With this as a control he studied 115 children who had been given prophylactic serum and found that 28% developed the disease.

Debré[39] gave injections of two to three cc. of pooled serum to 40 infants. Thirty one were completely protected, in six whooping cough developed, and three suffered from the disease in average intensity. Debré concluded that convalescent serum given during the period of incubation completely protected the exposed child; that given at the end of incubation period resulted in attenuation; and that given after the disease was well established had no great effect.

Bradford[40] ran a controlled series of cases exposed to pertussis in the family to determine the effect of convalescent serum and whole blood when given during the incubation period and during the catarrhal stage. When convalescent serum was given to 27 children in the incubation period, 15 or 55%, contracted whooping cough. Ten, or 66%, had a mild form, and one had a complication consisting of a mild form of tonsillitis in the sixth form. Of 20 controls all of whom developed the disease, eight, or 40% had a mild attack; four, or 20%, had complications consisting of otitis media, bronchitis and pneumonia. When given during the catarrhal stage, the resultant disease was about the same in the treated and control groups, except that the controls showed one pneumonia out of 13 cases.

Experimentally, Bradford[41] has contributed much fundamental research. He has shown that intra-tracheal inoculations of H. pertussis into a mouse would produce consistently uniform findings in the lungs. He has made use of investigations of humoral immunity in pertussis chiefly directed toward studies relating to specific agglutinins and complement-fixing antibodies. One direction his recent work has taken concerns the study of the opsonocytophagic reaction of the blood, as suggested by Veitch and applied by Huddleson[42].

The opsonocytophagic reaction is a test for the opsonizing antibody in the serum as well as for the phagocytosing power of the leukocytes. The technique of determining the opsonocytophagic reaction consisted of mixing 0.05 cc. of whole blood obtained as it flowed freely from a small incision in the finger tip, with 0.05 cc. of 1 to 1000 solution of heparin or physiological salt solution. To this was added 0.05 cc. of a standard killed (merthiolate 1-10,000) suspension of Phase I H. pertussis organisms containing approximately ten billion organisms per cc. The organisms were added within 30 minutes after the blood was withdrawn, the mixture was shaken and placed in a 37 degree C. water bath for 30 minutes. A second shaking was done after 15 minutes of incubation. At the end of the 30 minute period, without further shaking, smears were made, fixed with methyl alcohol, and stained by the Giemsa method for 20 minutes, washed, dried and examined under oil immersion.

A series of 25 consecutive polymorphonuclear leukocytes were examined and the organisms engulfed in each were counted. The cells were then classified according to the number of organisms engulfed. Three arbitrary groups were used to denote the degree of phagocytosis as follows:

None to slight . . . . . 0 to 4 organisms.
Definite . . . . . .5 to 19 organisms.
Marked . . . . . 20 or more organisms.

He studied this reaction during and after pertussis[43]. The table below shows the opsonocytophagic reaction of the blood during the course of pertussis:

Week of Disease	Number of Patients Tested	Distribution		
		0-4	5-19	20 plus
1 and 2	13	2.8	18	4.2
3 and 4	15	1.3	14.5	9.2
5 and 6	12	0.8	9.5	14.6
7 and 8	9	0.6	8.6	15.1

As convalescence approaches there is an increase in the cells in the 20 plus column and a decrease in the other two.

Comparing children of various age groups who gave no history of pertussis with those who gave a positive history of pertussis, it was shown that the latter had a higher opsonocytophagic index. It was noted, however, that older children gave a moderately high test because of the presence of normal opsonins.

Comparing the blood of mothers with that of their new-born babies, Bradford found that babies of mothers with a history of pertussis gave a higher test than the others. This suggests placental transfer of the antibody in certain instances.

In vitro experiments conducted along similar lines except for the addition of 0.05 cc. of immune adult serum increased the opsonocytophagic index markedly.[44]

In vivo experiments comparing the effect of transfusions and of whole adult blood and hyper-immune serum, gave similar response, that is, an increase in the number of cells showing marked phagocytosis.

Because of the increase in the opsonocytophagic reaction in the blood of individuals who have a history of pertussis and were subsequently hyperimmunized, this procedure has been recommended by Bradford to make available a group of donors for convalescent serum.

At a recent meeting of the American Pediatric Society[45], he reported his results and recommended highly the use of hyper-immune donors. He found that hyper-immune (lyophile) serum protected young mice against death from experimentally induced infection with H. pertussis, when the serum was injected at the same time that the organisms were administered.[46]

Thirty-two from a group of 40 treated mice survived, while only 4 survived from a group of 40 controls. The degree of lung involvement in the treated group was definitely less than in the controls. The difference between the groups in the number of mice showing negative lung cultures at autopsy was also statistically significant.

Sulfapyridine, in daily dosages of 20 mg. per mouse administered for three days failed to protect either three or six weeks old mice.

Combined treatment, consisting of sulfapyridine by mouth and immune serum by injection, protected both three and six weeks old mice, but the protection was no greater in the younger animal than that produced by the serum alone.

He also tested the effect of hyper-immune human serum (lyophile) upon the humoral antibody titre in pertussis.

A group of 19 infants and three children in the early stage of pertussis were treated by the intramuscular injection of from 10 to 40 cc. of hyperimmune human serum (lyophile).

In 19 of the group, the opsonocytophagic reaction and agglutinin titres of the blood were determined immediately before and after serum injection.[47] The humoral antibodies as measured by these methods were increased to levels

comparable to those characteristic of convalescence. A definite decrease in the absolute number of the lymphocytes of the blood was noted in 15 of the 22 cases, and there was apparent improvement in the clinical course of the disease in 18 of the 22 cases treated with the serum.

We are at present preparing hyper-immune serum by actively immunizing a group of medical students, all of whom give a history of pertussis. They are receiving three courses of vaccine injections at three months intervals.

PROPHYLAXIS AGAINST CHICKENPOX

The successful use of convalescent serum for prophylaxis of chickenpox has been reported by Blackfan, Peterson, and Conroy[48], Mitchell and Ravenel[49], Gordon and Meader[50], Lewis and Barenberg[51], and by several others. Chickenpox in children is a fairly inocuous disease, but it is source of difficulty in the pediatric ward. In the experience of Gordon and Meader, 68% of susceptible children exposed to chickenpox in a hospital and not treated contracted the disease.

These authors have pointed out that the protective properties of convalescent varicella serum diminish rapidly after three months following defervescence. Pooled adult serum secures complete protection in a moderate percentage of cases, but it is not so effective in prophylaxis against chickenpox as it is against measles.

McGuinnes, Stokes and Mudd[52] report the following results in prophylaxis against 157 cases:

	Convalescent Serum	
	No Disease	Clinical Case
Home Exposure	4	7
Hospital Exposure	47	1

	Pooled Adult Serum	
	No Disease	Clinical Case
Home Exposure	15	3
Hospital Exposure	71	14*

*6 of these cases were given inadequate dose of 7.5 cc.

These results are not conclusive and it cannot be said that chickenpox convalescent serum has been shown to prevent or modify the disease.

MUMPS

Alfred Hess[53] in 1915 first reported the use of convalescent serum for prophylaxis in mumps. Skrotskiy[54] reported the intramuscular injection of from five to 15 cc. of convalescent serum in 179 children exposed to mumps. In this group two mild cases developed, the remainder apparently being completely protected. Cambessedes[55] in 1933 reported the successful use of convalescent serum in prophylaxis and also considered that serum could be used to advantage in the treatment of the disease, by this means reducing the incidence of orchitis. Barenberg and Ostroff[56] used adult whole blood as well as convalescent whole blood in prophylaxis against mumps. Thirty-nine per cent of the control group developed the disease as compared with 15% of those injected.

Convalescent and pooled normal adult serum have been used by McGuinness, Stokes and Mudd[57]. Their results are tabulated as follows:

Prophylaxis Against Mumps in 140 Cases

	Convalescent Serum	
	No Disease	Clinical Case
Home Exposure	63	5
Hospital Exposure	15	12

	Pooled Adult Serum	
	No Disease	Clinical Case
Home Exposure	4	1
Hospital Exposure	48	2

Some of the failures were attributed to inadequate dosage or late administration. In a few cases the incubation period was prolonged so that the passive immunity may have worn off. Probably the greatest benefit from mumps convalescent serum is its use in adults as a prophylactic and a therapeutic measure against complications.

POLIOMYELITIS

In 1910, Landsteiner and Levaditi[58] effected in vitro, the neutralization of the virus of poliomyelitis by means of convalescent monkey serum. This finding was quickly confirmed and extended by other workers.

In the decade between 1915 and 1925, the mortality from poliomyelitis was between 15 and 25%. Naturally, the value of convalescent serum therapy seemed established in 1927 when Aycock and Luther[59] reported only one death in a series of 106 serum treated cases. However, the mortality was higher in the next series of cases reported by Aycock and his co-workers[60] in 1929.

Since 1930, the limitations of serological inactivation in vivo of viruses has been recognized. In experimental infection in monkeys it has been impossible to demonstrate any value for serotherapy and has been difficult to show that passive protection lasts for more than a day or two[61-65]. In vitro neutralization of the virus by immune serum continues to be demonstrable with considerable regularity, and by this means it has been shown that there are serologically distinct races of the virus[66-68]. This heterogenicity of strains casts doubt on the efficacy of convalescent serum in poliomyelitis. Moreover, in the preparalytic stage, the virus has in all probability already attacked the nerve cells, and once this fixation of virus and susceptible cell has occurred, it is not likely that serum can modify the disease.[69-70]

In the 1931 epidemic in New York, Brooklyn, and Hartford, it was felt justfiable to include untreated control groups.[71-76] The general results in all groups pointed in the same direction, namely that there was not much to be gained by serotherapy; and Park found that the use of a certain serum greatly increased the mortality (refined horse serum given intrathecally.)

Recently the subject of serum treatment in poliomyelitis has been reopened. The new evidence consists in the citation of three favorable series of cases: Cowie and his collaborators in Michigan; Jensen in Denmark; and Levinson in Chicago. None of these series were satisfactorily controlled; however, the work of Jensen deserves special mention. In the 1935 epidemic, Jensen collected serum from paralytic, non-paralytic, and abortive cases. Each type of serum was titrated for its protective value in monkeys and the following results were obtained:

(a) Serum from paralytic cases shows approximately 1000-2000 protective doses per cc.

(b) Serum from non-paralytic cases shows approximately 80,000 protective doses per cc.

(c) Serum from abortive cases shows approximately 150,000 protective doses per cc.

From these figures, it seems possible that serum from abortive cases of poliomyelitis with high antiviral titre may have some therapeutic value, if administered early in the disease before fixation of the virus with nerve cells has occurred.

DESSICATED AND CONCENTRATED SERUM AND PLASMA

The increased stability of biologic

substances in dry form has long been recognized. The development of a sterile, dry, readily soluble product in which the antibodies are preserved intact has been the culmination of experiments dating from the original studies of Ehrlich. In general, his method of preservation consisted of drying such products in vacuo and at low temperatures. However, dessication of products by this method results in a definite reduction of their specific biologic value. This reduction occurs during the drying process and is probably due to the action of salts and other agents which become effective when they attain a certain concentration. Once dried, however, whatever values still exist are maintained over a period of years if stored in vacuo.

In 1909, Shackell[80] described a method of drying relatively small amounts of biologic materials in the frozen state. He noted that the complement of guinea-pig serum, known to deteriorate when stored in the liquid state, could be preserved indefinitely by his method of preservation. The virus of hydrophobia, which is attenuated by Pasteur's ordinary manner of drying, retains its virulence when processed according to Shackell's technique. Observations had previously established the fact that many forms of life (vegetative forms, bacteria, germinating seeds) are not materially influenced even by exposure to the extreme cold of liquid air (-183 to -192 degrees Centigrade). (Brown and Escombe[81], Macfayden[82], Hammer[83], Rogers[84], and Swift.[85])

Practical apparatus and procedure for preserving biologics have been developed only within the past five years by Elser, Thomas and Steffen[86], and by Flosdorf and Mudd[87, 88]. The principle involves rapid freezing at low temperatures and rapid dehydration from the frozen state under vacuum. The dry porous material which results is called "lyophile" serum or plasma. In these products, the proteins are unaltered and their antibody properties are preserved intact. They may be kept for extended periods of time and may be redissolved in as little as one-fourth their original volume of liquid.

The properties of these "lyophile" products open up two special fields of possible application. First, since human convalescent serum can be preserved indefinitely by this process, it is available for immediate therapeutic or prophylactic use at any time. Second, the fact that lyophile serum or plasma can be redissolved in a much smaller volume of liquid than it originally contained has suggested the use of such concentrated substances in various altered physiologic states.

Several workers[89-92] have reported the use of lyophile convalescent serum in the prophylaxis and treatment of such acute infectious diseases as measles, scarlet fever, chickenpox, mumps, whooping cough, erysipelas, and streptococcic infections. The results obtained compare favorably with those reported by other investigators who have employed fresh serums or serums preserved in the liquid state. McGuinness, Stokes and Mudd[90] report moderately severe reactions (temperature of about 104 degrees, marked malaise, and local swelling and tenderness) in only five out of 1500 injections of lyophile serum, all symptoms starting within the first 6 hours after administration and lasting from 36 to 48 hours. Twelve cases had mild reactions of the same nature. Serum sickness such as frequently follows the administration of horse serum was not noted in any of this series. They conclude, with regard to reactions, that lyophile serum given intramuscularly causes no greater soreness than the same amount of fresh serum which has not been processed. The amount of serum and the concentration seemed to bear little relation to the severity of the local reactions. The most severe reactions followed the use of ten cc. or less of serum. As much as 80 cc. doubly concentrated has been given at one injection without any reaction whatever other than muscular tenderness lasting overnight.

"Lyophile" serum or plasma, doubly processed for intravenous use, has been tried by a number of investigators

clinically and experimentally. The application of concentrated preparations has been suggested for reduction of increased intracranial pressure, for treatment of traumatic and surgical shock, hemorrhage and severe burns, for correction of hypoproteinemia associated with wound disruption, for nephrosis, and for hypoproteinemia due to diarrhea, especially in infants.

Hughes, Mudd, and Strecker[93] report a small series of cases (7) in which concentrated serum was used for the reduction of increased intracranial pressure. They point out that concentrated blood serum approximates the theoretically ideal hypertonic solution for reducing intracranial pressure, in that it is essentially a solution which has a high osmotic pressure and contains solutes which will remain in the blood vessels after injection to exert a continued osmotic effect.

Their cases include five with cerebral neoplasm, one with subdural hematoma, and one with concussion. Intracranial pressures ranged from 220 and 440 mm. of water. Administration of from 40 to 100 cc. of serum concentrated four times in 50% glucose, was followed by pressure reduction varying from 95 to 275 mm., occurring over a period of 1 to 18 hours. Elevation of blood pressure and transitory increase in pulse rate was noted in all cases. No serum reactions were observed in this series.

A control series with normal intracranial pressure, receiving at weekly intervals 100 cc. each of serum regenerated in one-fourth its original volume of distilled water, in one-fourth the original volume using 50% glucose, showed lowering of intracranial pressure (25 to 70 mm.) following administration of the first two solutions, but no definite results from the use of glucose alone. They conclude that concentrated serum is effective in reducing intracranial pressure for relatively long periods of time, especially in those cases where the pressure is elevated above normal. This type of therapy is not recommended when any elevation of blood pressure may be dangerous.

A parallel series of experiments on dogs was conducted by Wright and Bond[94] in which cisternal puncture was done to obtain continuous readings of intracranial pressure. Their results indicate that a single administration of concentrated serum may produce lowering of increased intracranial pressure for as long as 20 hours.

The treatment of shock with concentrated blood serum is so far entirely experimental. In experiments on dogs by Wright and Bond[95], two groups of animals were used, one receiving isotonic saline and acacia; the other, hypertonic serum (four times concentrated). A comparison of similarly shocked animals showed that serum in equivalent dosage was more effective than acacia in raising and maintaining the blood pressure. In conclusion they point out that their experimental data suggest the possible use of lyophile serum in the treatment of traumatic and surgical shock, severe burns, and hemorrhage.

The restoration of serum protein values and elevation of the oncotic pressure of blood serum for the dehydrating effect on localized or generalized collections of intracellular fluid has been attempted in nephrosis by using concentrated serum. In 1938, Aldrich et al.[96] reported that this type of serum in doses of 80 to 315 cc. was given to nine patients with lipoid nephrosis and edema. Some diuretic effect resulted from its use, but the method was not entirely satisfactory since this type of treatment failed in three of the nine cases. In the remaining six cases, complete and immediate diuresis took place and four of this group not only lost their edema but had normal urine within a few weeks. Patients with favorable response lost weight in a manner similar to that in which weight is lost in a spontaneous renal crisis. This may mean that in some way such a process is initiated by this type of treatment. Intravenous administration of lyophile serum has occasionally been associated with severe reactions in nephrotic children.

Thalhimer[97] has devised a simple pro-

cess for concentrating normal serum by which it is reduced to one-third, one-fourth, and one-fifth its original volume by evaporation in viscose casings. Serum prepared in this way can be put to any of the uses mentioned previously. He has also used his concentrated serum for treatment of edema associated with protein deficiency due to diarrhea in infants. Reports of his work are not yet available.[98]

Investigators [99,100] of the causes of disruption of abdominal wounds have pointed out that experimentally, at least, and probably clinically a state of hypoproteinemia may be one of the factors which retards the normal healing. Eleven dogs in whom a state of protein deficiency was induced were subjected to abdominal laparotomy. In eight of these, disruption of the wound or failure of the incision to heal was observed. Subsequent experiments demonstrated that normal healing of the wound occurred when the hypoproteinemia was controlled by intravenous infusion of lyophile plasma. Concentrated plasma is thought to have two advantages: it rapidly corrects the deficiency of blood proteins; and being a hypertonic solution, increases the osmotic pressure of the blood and tends to overcome any tissue edema which may be present.

USE OF HUMAN PLASMA IN HEMOPHILIA

The recent investigations of Patek and Stetson[101] indicate the defect in coagulation of blood in hemophilia resides in the plasma rather than in the platelets. Consequent upon this observation, Patek and Taylor[102,103] have isolated from citrated normal cellular-free plasma, by iso-electric precipitation, which is associated with the clot-promoting factor of normal plasma. This material, called "globulin substance" is quantitatively effective both in vitro and after intravenous injection, in reducing the coagulation time of hemophilic blood. Intravenous administration reduced the clotting time in three cases from 135, 150 and 165 mknutes to 24, 25, and 30 minutes within three hours. Following this, the clotting time rose gradually to reach pre-injection levels within 24 to 48 hours.

Pohle and Taylor[104] using this same globulin substance intramuscularly obtained a favorable response in all their cases. There was a sharp fall in coagulation time to minimum levels in from one-half to one hour after injection, the low value being sustained for several hours and returning to pre-injection heights after 24 hours.

Observations with repeated intramuscular or intravenous injections of globulin substance strongly indicate that there is a refractory phase which develops after the first injection. It appears that during such a phase the coagulation time of the blood in hemophilia increases although the concentration of the globulin substance in the circulating plasma is not diminished. The refractory period is not longer than 24 hours since an injection at this time gives the optimal effect. Actual cause of the refractory period and its nature is not yet known.

SUMMARY AND CONCLUSIONS

1. Human convalescent serum is a definitely valuable therapeutic agent in combatting the toxemia of scarlet fever and in reducing the complications. Immune substances other than antitoxin are present in scarlet fever convalescent serum in demonstrable amounts and may contribute to the effectiveness of the serum. The value of immune serum for prophylaxis of scarlatina is not yet definitely established.

2. Serum transfusions for septicemia are suggested as a possible form of therapy.

3. Measles convalescent serum is successful prophylactically in a high percentage of cases. The use of serum for treatment of the disease must be further investigated before definite conclusions can be drawn.

4. It is difficult to evaluate the effect of immune serum in pertussis.

At present, evidence points toward the use of hyperimmune serum as the most probably effective prophylactic measure.

5. The value of varicella immune serum has not been established conclusively.

6. Probably the greatest benefit from mumps immune serum is its administration to adults for prophylaxis and for treatment against complications.

7. Clinical uses for concentrated serum and plasma are suggested. This is a new field and extensive investigations will be necessary to ascertain the value of such biologic materials.

8. Cases of hemophilia have been treated with normal human plasma. At present the results seem favorable, but definite conclusions cannot be formed from its use in small series of cases.

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V. GOSSIP

Ray M. Amberg, Superintendent of the University of Minnesota Hospitals was named President-elect of the Minnesota Hospital Association in St. Paul at their annual meeting last week. Congratulations! ...The postgraduate course for operating room nursing supervisors held at the Center for Continuation Study on Monday, Tuesday, and Wednesday, May 22, 23, and 24, attracted the largest registration of the medical and hospital courses when 110 nurses came. It was necessary to use 5 buses for the field trips to Minneapolis and St. Paul. Nurses were in attendance from Minnesota, North and South Dakota, Montana, Wisconsin, Iowa, Nebraska, Manitoba and Colorado. Valborg Hedback of the Red Cross Hospital, Helsingfors, Finland, who was visiting in Minneapolis added the long distance touch. Bacteriologist Thomas B. Magath of the Mayo Foundation was the "ask me another" man of the course as the ediphones transcribed an hour lecture on sterilization and two hours of questions and answers. Because of the success of this course requests have been received for similar instruction in obstetric and pediatric nursing...The University of Minnesota is well represented in the exhibit section at the annual meeting of the Minnesota State Medical Association meeting this week in Minneapolis. S. A. Weisman (quinidine), J. B. Carey, R. S. Ylvisaker and N. Logan Leven (gastroscopy), Walter H. Fink (ocular dynamics), Arthur D. Hirschfelder (sulfanilamide), Raymond N. Bieter, W. P. Larson, E. B. Cranston and M. Levine (chemotherapy), Harold N. Wright (mapharsen and arsphenamine) (digitalis) (flavoring drugs), Ancel Keys and H. L. Friodell (roentgen kymography), Jos. T. King and August F. Henschel, (tissue cultures and sulfanilamide), Raymond N. Buirge, Clarence Dennis, Richard Varco, O. H. Wangensteen (appendicitis), Harry Hall, Charles E. Rea (transfusion and shock), Charles E. Rea, Hanns C. Schwyzer, B. A. Smith, Jr., O. H. Wangensteen (intestinal obstruction), Carl W. Waldron, S. G. Balkin (reconstructive surgery), Paul F. Dwan, E. S. Platou (human serum), W. A. O'Brien (post-graduate medical education). In addition there will be University exhibits by the Mayo Foundation, Gillette State Hospital for Crippled Children, Glen Lake Sanatorium, Lymanhurst Clinics, and the Division of Veterinary Medicine. There will be demonstrations of scientific cinemas and papers by the following medical school representatives: V. P. Hauser, W. D. White, E. C. Henrikson, E. J. Engberg, G. N. Ruhberg, Louis Sperling, H. E. Michelson, E. M. Rusten, J. L. McKelvey, Hamlin Mattson, F. E. B. Foley, L. R. Boies, N. Logan Leven, H. A. Carlson, M. H. Hoffman, W. A. O'Brien, and F. S. Chapin (sociology). The following from the Medical School faculty will preside at round table luncheons: R. N. Bieter (newer drugs), O. H. Wangensteen (surgery of the small bowel), C. J. Ehrenberg (treatment of sterility), R. V. Ellis, (allergy), H. E. Richardson (medical emergencies), C. A. Stewart (contagious diseases), and J. M. Hayes (surgery of the gall bladder). In addition we are represented in the officers and councilors of the association, delegates to the American Medical Association, Committee on Scientific Assemblies, Committee on Local Arrangements, and in practically all the committees which function through the year. The University of Minnesota is playing a very prominent part in the public health exhibition which is being held in the basement of the Minneapolis Auditorium. The hours are 10:00 A.M. to 10:00 P.M. daily from Wednesday to Saturday. It is to be noted that the schedule does not follow the regular scientific and economics meeting. The University of Minnesota and the medical profession of our State enjoy working together for we are one. Committees from medical associations in other states report that we are fortunate both from the standpoint of the University and from that of the profession. At a recent meeting of the Public Relations Committee of the State Medical Association (University Affairs), it was pleasant to note the ability to discuss issues frankly and impersonally. This ideal arrangement has not come about through chance. It is the direct result of the University and the profession being able to see the other fellow's problems. The University of Minnesota Hospitals enjoy the confidence of the profession at large. It is up to all of us to see that this condition continues.....

UNIVERSITY OF MINNESOTA

CENTER FOR CONTINUATION STUDY

Postgraduate Medical and Hospital Courses

Summer and Fall, 1939

July 17-22. Electrocardiography. For physicians who use electrocardiographic methods in the diagnosis and treatment of heart disease. A special feature will be the division of the group into small sections for instruction in reading tracings.

July 31-August 5. Clinical Allergy. For physicians especially interested in the recognition and relief of allergic disorders in various parts of the body. There will be demonstrations of the effects of the disease in different age periods.

August 31-September 2. Medical Technology. A special three-day course in new and approved laboratory procedures for registered medical technologists and others eligible for registration. Not a beginners' course.

September 25-30. Proctology. A limited registration course in the diagnosis and treatment of diseases of the anorectal region. First consideration will be given to the large number of registrants who failed to obtain places in previous courses.

September 25-30. Urology. A course for urologists, surgeons, and others interested in diagnosis and treatment of genitourinary diseases. It is probable that the program will be limited to two or three subjects within the field.

October 9-11. University of Minnesota Clinics. For general practitioners and others. A three-day intensive program of demonstrations in the various fields of medicine. Registration limited to the number who can be accommodated by the facilities of the Medical School.

October 12-14. Fiftieth Anniversary of Founding of Medical School. Program by scientists from the United States and other countries presenting the significant advances in biochemistry and physiology as they relate to medicine. No registration limitation or fee.

October 16-21. Nursing Education. A study program for nursing educators and their assistants will be held during the special commemoration week of the founding at the University of Minnesota of the first university school of nursing in the United States.

October 30-November 1. Hospital, Medical, and Institutional Librarians. A study course in bibliotherapy. For special librarians who supply reading service to patients, and other librarians who may be interested in hospital book service.

November 6-11. Cardiology. A course for physicians interested in the diagnosis and treatment of diseases of the heart. One of our most popular courses when first offered two years ago. The new program will include all the recent advances made in this field.

Other Summer and Fall Courses May Be Arranged.
See Special Announcements.

FUTURE COURSES

Courses will be offered during the summer, fall, winter, and spring months. If they can be arranged, special courses will be given when a sufficient number of physicians and hospital personnel request them. From January 1, 1937 to May 31, 1939, the Center for Continuation Study has given 37 courses in postgraduate medical and hospital education to 1,182 registrants from Minnesota and surrounding states. Since July 1, 1939 the program has been aided by a special grant from the Commonwealth Fund, New York City. The Center is an ideal place to spend a short time in intensive study in a special field under a most economical arrangement of "living and learning" under one roof.

Further information from J. M. Nolte, Director, Center for Continuation Study, and William A. O'Brien, M.D., Director, Department of Postgraduate Medical Education, University of Minnesota, Minneapolis.