THE INTRAVENOUS USE OF SERUM AND PLASMA, FRESH AND PRESERVED*

MAX M. STRUMIA, M.D., JOSEPH A. WAGNER, M.D.
AND
J. FREDERICK MONAGHAN, M.D.
BRYN MAWR, PA.
FROM THE BRYN MAWR HOSPITAL, BRYN MAWR, PA.

THE INTRAVENOUS USE of serum and plasma in place of whole blood is not new. The number of contributions on this subject has greatly increased in the last few years.

One of us has been interested in this problem intermittently since early 1927, at which time human serum was intravenously administered in cases of severe infections, especially those of streptococcic origin. It was noted then that the intravenous administration of serum in sufficiently large quantities (50 to 100 cc.) was commonly followed by reactions, often very severe, even when the sera were homologous, *i.e.*, caused no agglutination of the erythrocytes of the recipient. For serum, in this paper, is meant the fluid portion of the blood separated after clotting. Later (1929–1930), citrated blood was centrifuged and the plasma employed instead of serum. Primarily, this method was adopted because of its simplicity and its greater yield of the fluid portion. It was then noticed that the plasma, intravenously administered, caused no reactions, even when no attention was paid to typing. As a precaution the plasma was diluted with equal parts of saline solution before administration. We did not know at that time that this behavior of blood serum and blood plasma had already been observed and studied by Brodie,[1] as early as 1900. He found that, in cats and other experimental animals, the intravenous injection of blood serum, even autogenous, commonly produced reactions, which did not occur when similar quantities of sodium citrate plasma were used.

Of recent years, the intravenous injection of blood plasma in place of whole blood has been made the object of intense study by the Staff of the Bryn Mawr Hospital. Both serum and plasma have been used in infections,[2] in the prophylaxis and treatment of nutritional hypoproteinemia and anemias resulting therefrom,[3] in burns,[4, 5, 6] in certain hemorrhagic and hemolytic diseases, in preeclamptic states, in liver disease,[7] in chronic colitis, and, finally, in secondary shock.[8]

It is not the purpose of this communication to evaluate the clinical results of the use of plasma in the various conditions enumerated nor to discuss the

* This investigation was aided by a special Research Fund established by the Women's Board of the Bryn Mawr Hospital. Submitted for publication February 12, 1940.

rationale of whole blood transfusion, but rather to emphasize the simplicity of preparation and the safety in its use as compared to whole blood, and to make certain comparisons with the use of serum, both fresh and preserved.

The blood is collected in a closed system (Fig. 1), employing as an anti-coagulant 2 per cent sodium citrate solution in saline in proportion of 100 cc. for each 500 cc. of blood. The citrate-saline solution is first drawn into a

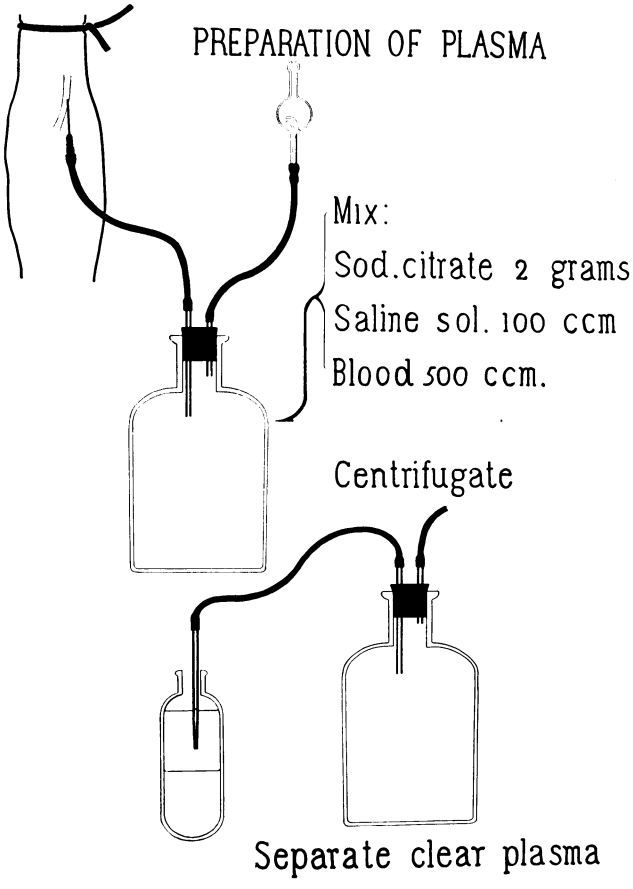

FIG. 1.—Showing the set-up for the collection of blood by a closed system.

liter pyrex flask by suction. The blood is then collected, using a rather large needle (No. 15–16 gauge) with the aid of slight suction. The flask is gently and continually rotated during collection, to insure thorough mixing of the blood with the citrate-saline solution. The plasma is separated by centrifuging the citrated blood for about one-half hour at high speed (2,000 r.p.m.). When considerable quantities of plasma are to be prepared, it is convenient to use a large centrifuge, holding four 250 cc. rubber-capped glass containers. The

opalescent supernatant plasma is removed by suction in a closed system and is stored at 4° C. The average yield of plasma is a little over 50 per cent of the citrated blood employed, not including the added citrate-saline solution. If the plasma is to be kept more than one day before being used, it is advisable to add "Merthiolate" 1:10,000 as preservative. On standing, there occurs, at times, a flocculent precipitate which is readily removed by short centrifugation. It does not, however, cause reactions if not removed. If the blood is collected after a meal, a buff layer of lipoid substance will, on standing, rise to the surface of the plasma. This material need not be removed, as it causes no reactions, and is easily resuspended by gentle shaking before administration.

Contrary to the statement of Lehman,[9] and others, it is not necessary, in our experience, to type the citrated plasma prior to the intravenous administration. Elliott[10] reached the same conclusion. As a rule we dilute the plasma with equal parts of saline or saline-glucose solution before injection, and regulate the speed of administration from 5 to 10 cc. per minute. When for particular reasons the bulk of fluids is to be limited, undiluted plasma may be safely administered. In such cases we regulate the speed of injection not to exceed 5 cc. per minute. The speed of administration does not seem to be, within certain limits, an essential factor, unless there exists a clinical contraindication. Undiluted plasma has been given in emergency cases at the rate of 8–10 cc. per minute without reaction. Viscosity of the material prevents administration at greater speed when the usual gravity method and a small size needle (No. 19–20 gauge) are employed.

Plasma thus administered has proved its complete safety and absence from reactions in over 1,500 administrations. One very important feature is that it can be given in very large and repeated doses. In one instance as much as 7,300 cc. were given in 11 days to a patient with severe burns, in an effort to maintain the serum protein concentration of the blood at a normal level. As much as 950 cc. of undiluted plasma were given as a single dose, followed immediately by 450 cc. of whole blood, without reaction. Intravenous injections of citrated plasma, fresh and preserved, have been repeated at intervals of three weeks, or longer, without reaction.

In 1935, Elser, Thomas and Steffen,[11] and, later, Flosdorf and Mudd[12] published reports on the procedure for the preservation in the lyophile form of serum and other biologic substances. Serum preserved in the lyophile form has been employed intravenously following regeneration with sterile water in the treatment of nephrosis by Aldrich, *et al.*,[13] and Jeans,[14] for the reduction of increased intracranial pressure by Hughes, *et al.*, [15a, b] and in hypoproteinemias by Ravdin.[3] It has been suggested from experimental work upon animals by Bond and Wright,[16] that the use of regenerated lyophile serum would be of benefit in hemorrhage and traumatic shock. Mahoney,[17] employing lyophiled plasma, reached the same conclusion after similar experiments. Thompson, *et al.*,[18] used lyophiled plasma to prevent hypoproteinemias and wound disruption in experimental animals.

Intravenous administration of lyophiled serum is often followed by reactions. Thus, Aldrich, *et al.*,[13] noted reactions to intravenous administration of lyophiled serum, which in two out of nine cases were severe and accompanied by chills and high temperature. Lehman[9] reported reactions with similar material, as does Ravdin.[3] In our experience, the intravenous administration of lyophiled serum has often been accompanied by severe reactions, even with as little as a 5 cc. dose. These reactions have been generally attributed to a change induced in the serum by the lyophile process. Our experience with fresh serum, related above, led us to investigate the use of lyophiled plasma. Citrated plasma, separated in the manner above mentioned, and lyophiled by the method of Flosdorf and Mudd,[19] was regenerated with sterile water to restore its original volume and administered intravenously to patients in quantities up to 100 cc. without reactions. This material was then employed in greater quantities in isotonic form and also in the hypertonic form, *i.e.*, concentrated as much as five times, still without reaction. The following is an abstract of a typical case:

Case Report.—A white woman, age 82, weighing 63 Kg., was admitted to Bryn Mawr Hospital with amebic dysentery. During the convalescence the patient developed hypo-albuminemia, with generalized pitting edema and oliguria. She was given, intravenously, citrated, lyophiled plasma regenerated with distilled water to only one-fifth of its original volume (125 cc., corresponding to 625 cc. of undiluted plasma). The lyophiled material had been preserved for several months. The plasma was administered by the drip method, during a period of 20 minutes. There was no reaction. The urinary output exceeded the intake for a period of three days following the administration of plasma. Within 48 hours, the edema had disappeared and in six days, when again checked, the blood albumin concentration rose from 2.6 Gm. per cent to 3.2 Gm. per cent.

In other cases, concentrated lyophiled plasma was administered at even greater speed, up to 110 cc. of five times concentrated solution (corresponding to 550 cc. of undiluted citrated plasma) in six minutes, without reaction. It is to be noted that concentrated lyophiled plasma appears as an opaque, amber, viscid fluid and that, to obtain the speed of transfusion mentioned above, a syringe must be used. We do not advocate rapid administration except in emergency cases, but we report it to emphasize the safety of the material. The method of choice for injection is the drip method, at a rate of about 4–5 cc. per minute.

COMMENTS AND DISCUSSION.—It may be accepted as a fact that intravenous administration of serum, fresh or preserved by the lyophile process, is often followed by severe reactions. These reactions were not encountered, in our experience or in that of other workers, *etc.*,[4, 5, 10, 20] when citrated plasma, separated by centrifugation, is employed, fresh or preserved, either by refrigeration or by the lyophile process. We do not intend to discuss the physiochemical differences between the serum and plasma responsible for the mentioned difference in behavior. We may assume, with Brodie,[1] that the difference is brought about by the process of fibrin precipitation. Reactions often

occur when citrated blood in which, accidentally, clotting has taken place, is injected intravenously. Filtration to eliminate blood clots does not prevent reactions.[26]

It is unfortunate that, in many reports, the terms "serum" and "plasma" appear to be used interchangeably. For instance in the article of Mahoney,[17] Bond and Wright[16] are quoted as having employed lyophiled plasma. Bond and Wright used lyophiled serum only in their investigative work.[21] Similarly, McClure[6] appears to use the two terms interchangeably.

In the ordinary type of hospital the lyophiling of plasma is not necessary, due to the fact that plasma keeps well under ordinary conditions of refrigeration (about 4° C.) for several months, except when used for its prothrombin and complement content. The content of specific antibodies in the plasma remains unchanged for at least 32 days;[22] the complement activity begins to decline only after the third and fourth week,[22] in a manner similar to that reported for refrigerated blood.[23] The period of useful survival of prothrombin was found to be one week to ten days,[22] similar to that found for the refrigerated blood by Rhoads,[24] and Lord.[25]

Plasma preserved at 4° C. has been employed successfully after 40 days, in the treatment of secondary shock[8] and various forms of hypoproteinemias. It is presumed that blood plasma can be preserved by refrigeration for much longer periods of time. Thus, plasma has been kept for three to four months in the frozen state, and then employed intravenously, without reaction. Refrigeration at 4° C. is probably as effective as freezing as a means of preservation, but technically much simpler.

In the Bryn Mawr Hospital, the plasma is a by-product of the blood bank. Experimental data[22] suggest that refrigerated blood is useless, occasionally dangerous, after five days of preservation. Citrated blood after five days of storage is centrifuged, the plasma pooled, dated and preserved. This keeps a fresh supply on hand for use in the conditions outlined previously. The lyophile method of preservation would, obviously, be of value in isolated hospitals, in cases of emergency in outlying districts, involving field work; disasters of many sorts, such as fires, flood, earthquakes, war, *etc.*,[20, 27] and for cases in which hypertonic plasma is indicated. We have employed lyophiled plasma kept for a period of ten months without reactions; it can, in all probability, be kept for a much longer period of time.

CONCLUSIONS

The intravenous use of citrated blood plasma without cross-matching is both safe and convenient. This applies to fresh plasma, or plasma preserved by either refrigeration at 4° C. or the lyophile process. Serum, separated after clotting, may cause reactions, often severe, when intravenously injected, whether employed fresh or preserved by either refrigeration or the lyophile process.

Appreciation is expressed to the Staff of the Bryn Mawr Hospital for their helpful cooperation and, especially, to Dr. D. D. Bond for valuable aid.

REFERENCES

[1] Brodie, T. G.: The Immediate Reaction of an Intravenous Injection of Serum. Jour. Physiol., **26**, 48, 1900.

[2] Nicholson, P.: Notes on the Treatment of an Unusual Case of Hemolytic Streptococcus Septicemia. Jour. Ped., **8**, 363, 1936.

[3] Ravdin, I. S., Stengel, A., Jr., and Prushankin, M.: The Control of Hypoproteinemia in Surgical Patients. J.A.M.A., **114**, 107, 1940.

[4] Elkinton, J. R., Gilmour, M. T., and Wolff, W. A.: The Control of Water and Electrolyte Balance in Surgical Patients. ANNALS OF SURGERY, **110**, 1050, 1939.

[5] Elkinton, J. R.: The Systemic Disturbances in Severe Burns and Their Treatment. Bull. of the Ayer Clin. Lab. Penna. Hosp., **3**, 279, 1939.

[6] McClure, R. D.: The Treatment of the Patient with Severe Burns. J.A.M.A., **113**, 1809, 1939.

[7] Tumen, H. J., and Bockus, H. L.: The Clinical Significance of Serum Protein in Hepatic Disease. Am. Jour. Med. Sci., **193**, 788, 1937.

[8] Strumia, M. M., and Wagner, J. A.: The Use of Citrated Plasma in the Treatment Secondary Shock, J.A.M.A., May, 1940.

[9] Lehman, E. P.: A Simple Method of Plasma Transfusion. J.A.M.A., **112**, 1406, 1939.

[10] Elliott, J.: A Preliminary Report of a New Method of Blood Transfusion. South. Med. and Surg., **98**, No. 12, 643, 1936.

[11] Elser, W. J., Thomas, A. R., and Steffen, G. I.: Desiccation of Sera and Other Biologic Products, Including Microorganisms, in the Frozen State, with Preservation of the Original Qualities of Products So Treated. Jour. Immun., **28**, 433, 1935.

[12] Flosdorf, E. W., and Mudd, S.: Procedure and Apparatus for Preservation in Lyophile Form of Serum and Other Biologic Substances. Jour. Immun., **29**, 389, 1935.

[13] Aldrich, C. A., Stokes, Jos., Jr., Killingsworth, W. P., and McGuinnes, A. C.: Concentrated Human Blood Serum as a Diuretic in the Treatment of Nephrosis. J.A.M.A., **11**, 129, 1938.

[14] Jeans, P. C.: The Use of Lyophile Serum. Jour. Iowa St. Med. Soc., **29**, 64, 1939.

[15a] Hughes, Jos., Mudd, S., and Strecker, E. A.: Treatment of Increased Intracranial Pressure by Concentrated Human Lyophile Sera. Trans. Am. Neurol. Assn., **62**, 118, 1936.

[15b] Hughes, Jos., Mudd, S., and Strecker, E. A.: Reduction of Increased Intracranial Pressure by Concentrated Solution of Human Lyophile Serum. Arch. Neurol. and Psych., **39**, 1277, 1938.

[16] Bond, D. D., and Wright, D. G.: Treatment of Hemorrhage and Traumatic Shock by the Intravenous Use of Lyophile Serum. ANNALS OF SURGERY, **107**, 500, 1938.

[17] Mahoney, E. B.: A Study of Experimental and Clinical Shock with Special Reference to Its Treatment by the Intravenous Injection of Preserved Plasma. ANNALS OF SURGERY, **108**, 178, 1938.

[18] Thompson, W. D., Ravdin, I. S., Rhoads, J. E., and Frank, I. L.: Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption. Arch. Surg., **36**, 509, 1938.

[19] Flosdorf, E. W., and Mudd, S.: An Improved Procedure and Apparatus for Preservation of Sera, Microorganisms and Other Substances—The Cryochem Process. Jour. Immun., **34**, 469, 1938.

[20] Brodin, P., and Saint Girons, F.: Plasma Transfusion. J.A.M.A., **113**, 2072, 1939.

[21] Bond, D. D., and Wright, D. G.: Personal communication, 1939.

[22] Strumia, M. M.: The Fate of Transfused Refrigerated Blood. (In course of publication.)

[23] Kolmer, J. A.: Preserved Citrated Blood "Banks" in Relation to Transfusion in the Treatment of Disease with Special Reference to the Immunologic Aspects. Am. Jour. Med. Sci., **197**, 442, 1939.

[24] Rhoads, J. E.: Prothrombin Time of Bank Blood. J.A.M.A., **112**, 309, 1939.

[25] Lord, J. W., and Pastore, J. B.: Plasma Prothrombin Content of Bank Blood. J.A.M.A., **113**, 2231, 1939.

[26] Wiener, A. S.: Blood Groups and Blood Transfusion. Charles C. Thomas, Baltimore, 1935.

[27] Tatum, W. L., Elliott, J., and Nessett, N.: A Technique for the Preparation of a Substitute for Whole Blood Adaptable for Use during War Conditions. Military Surgeon, **85**, 481, 1939.