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Plasma transfusion in circulatory failure

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PLASMA TRANFUSION IN CIRCULATORY FAILURE.

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I
INTRODUCTION

The therapeutic value of whole blood, blood plasma or serum transfusion depends upon certain fundamental physiologic principles which may be outlined as follows (1) increase in fluid volume of circulating blood, (2) immediate increase in the oxygen-carrying capacity of the blood, (3) increase in protein concentration of blood, (4) increase in the congulability of the blood, (5) possible stimulation of hematopoiesis, and (6) addition of immunologic factors.

It is now well established that diminished circulating blood volume is one of the most significant features in peripheral circulatory failure or shock due to hemorrhage, trauma, or other causes. For a better comprehension of the rationale of transfusion, it may be desirable to consider briefly some of the factors involved in hemorrhage which has been controlled although there is usually a dilution of the blood. This is the result of a compensatory mechanism in which there is widespread peripheral vasoconstriction and an immediate and prompt transfer of fluids from the tissues to the vascular system. (41) Under these circumstances the decrease in circulating blood volume is so trasient that no sifnificant consequences occur. However, if

the hemorrhage is severe, the compensatory mechanism may not be sufficient to counteract the diminished blood volume and peripheral circulatory failure may result. Accordingly, as emphasized by Blalock, (6) the loss of whole blood becomes "the main initiating agent in the causation of circulatory failure," and "the term 'shock due to hemorrhage' describes the condition." Whereas the main initiating factor in this type of peripheral circulatory failure is the loss of whole blood, in other types it is the loss of plasma. As stated by Blalock, (6) "It simply happens that in hemorrhage the injury to vessels is such that whole blood is lost whereas in 'plasma loss' the direct damage to capillaries or the increase in permeability from indirect causes allows the escape of a much larger proportion of plasma than of red blood cells." There are undoubtedly other initiating factors in the causation of peripheral circulatory failure, but no attempt will be made here to discuss these, as they have been adequately reviewed by Blalock, (6) in his thorough dissertation of this subject. Suffice it to say that the most significant factor in peripheral circulatory failure, no matter what the cause, is the diminished circulatory blood volume. Once this has developed,

there are a number of sustaining factors which operate in a vicious circle. These have been excellently summarized by Blalock. (6) As a result of the diminished circulating blood volume, the tissues receive an inadequate supply of oxygen. The resultant anoxia not only causes damage of tissue in general but produces increased capillary permeability with further loss of plasma. As a result of circulatory retardation, there is marked impairment of renal function and consequent disturbance of acid base equilibrium. The increased concentration of blood, with consequent retardation of blood flow in the capillaries, thus decreasing the return flow to the heart and further diminishing the circulating blood volume. The final consequence of this series of events is marked tissue anoxemia and death of the organism.

It becomes obvious, therefore, that a diminished circulating blood volume is one of the most significant factors in peripheral circulatory failure or shock due to hemorrhage, trauma, or other causes. Accordingly the rational treatment of such a condition is based upon an attempt to produce a prompt return to normal of the circulating blood volume and to maintain it at this level. The most effective means of accomplishing

this is by the intravenous administration of a fluid which would not only supplemnet the blood volume but would also maintain it. It should be realized that in such states as described above there is a depletion of plasma proteins which are essential in maintaining osmotic pressure and therefore in holding fluids in the vascular tree and attracting them from the tissues. For this reason, the addition of a noncolloidal solution, such as isotonic salt solution, merely dilutes the plasma proteins, with consequent diminution of the osmotic pressure, resulting in a greater and more rapid escape of fluid from the vessels. This is further enhanced by the increased permeability resulting from capillary damage by anoxia which is a frequent occurrence in these conditions. Thus, the intravenous injection of noncolloidal solutions produces only a transient increase in circulating blood volume and the state of shock soon returns. Since the classic observations of Starling of the importance of organic and colloidal constituents of the blood in maintenance of normal colloidal osmotic pressure, these facts have been emphasized repeatedly by experimental and clinical investigations.

It is now well established that one of the important

effects of blood transfusion is its substantial increase and maintenance of circulating blood volume, especially in the presence of a previously depleted vascular system. Numerous clinical and experimental observations attest to the fact that no other substance can act in this manner as efficaciously as blood. Because of certain inherent disadvantages to the use of blood, various attempts have been made to use a substitute fluid more readily available. These include, besides saline and other salt solutions, glucose solution, gelatin and gum acacia solutions, ascitic fluid, amino acid mixtures, hemoglobin-Ringer solution and hemolyzed blood, and blood plasma and serum. The reader interested in a more detailed discussion of some of these substitutes should refer to the recent review of Amberson whose conclusion agrees with the generally accepted fact that "there is no complete substitute for blood." With the exception of plasma or serum, which strictly speaking does not belong in this category of substitutes, none of the substances mentioned above has proved wholly satisfactory. In fact, there is considerable evidence of their deleterious effects.

As previously stated, blood plasma or serum strict-

ly speaking cannot be considered substitute fluids because they contain practically all the fluid elements of whole blood. For this reason, they should be truthfully considered in the category of whole blood as far as this discussion is concerned. Plasma was the only substance which gave results approximating those obtained with whole blood.

However, in blood depletions other than anemia, the administration of the fluid element of the blood, i.e. blood plasma or serum, may be just as effective and in some states even more rational. Thus, in peripheral circulatory failure due to local trauma or visceral exposure and in burns there is "Plasma loss" and usually hemoconcentration. In such states the diminution in blood volume is more effectively corrected by the transfusion of plasma rather than whole blood because the addition of red cells is not only unnecessary, but theoretically might be harmful. It should be realized, of course, that even in peripheral circulatory failure due to hemorrhage the transfusion of plasma or serum is also beneficial and effective because in such a condition the most pressing need is the restoration of circulating blood volume. (8)

There are a number of practical advantages to the

use of blood plasma or serum over whole blood. In transfusing whole blood it is necessary to obtain a suitable donor, which requires compatibility and serologic tests. These are time-consuming procedure which in emergencies may be significant. Moreover, the availability of donors is an important factor to consider, especially in military practice. These difficulties can be readily obviated by the use of plasma or serum. By adequate preparation they may be stored for long periods without deterioration and be ready for instant use. Preliminary typing and compatibility tests are unnecessary because isoagglutinins are partially suppressed by pooling and further inhibited by the patient's blood. (36) Although the use of plasma and serum has only recently received intensive consideration as a substitute for the use of blood, it should be realized that studies of this nature have been carried on for a number of years.

II

HISTORY OF PLASMA TRANSFUSION

Blood plasma as a substitute for whole blood was suggested as early as March, 1918 by Gordon R. Ward (27) in England. He pointed out that one of the chief troubles with whole blood was that the recipient's plasma

might hemolize the corpuscles of the donor. He made the observation that death from hemorrhage was not due to lack of hemoglobin but from loss of fluid, and thus the great need in these patients for the replacement of the depleted fluid. He suggested that this could be done by the administration of citrated plasma which could be preserved easily and injected safely.

Rous and Wilson (48) in 1918, while working on hemorrhage in animals, used plasma to replace the blood lo loss. As a result of their experiments they pointed out that the replacements of red blood cells is not essential because even in severe hemorrhage a sufficient number of cells remains to support life. The loss of blood volume is the important factor. Following gross hemorrhage they were able to restore the blood pressure to normal and maintain it by replacing the removed blood with an equal quantity of plasma.

Mann, (39) in 1918, discussed the use of serum for treating surgical shock produced experimentally in dogs. He noted that the parenteral injection of homologous serum produced results which were as good or even better in the treatment of experimental shock than any other method at his disposal. It is worthy of mention that his best results were obtained with relatively large doses of serum. He asserted that homologous serum

might be of value under conditions where serum could be kept and whole blood could not be obtained.

Strumia (53) began using human serum intravenously in 1927 for the treatment of severe infections. Later in 1927 he began using plasma because of its simplicity of preparation and its greater yield. It was noted then that even heterclogous plasma given intravenously caused no reactions whereas homologous serum commonly caused severe reactions. This difference in behavior of plasma and serum had previously been observed and commented on by Brodie (10) in 1900. Untoward reactions from serum were thought by him to be due to the process of fibrin precipitation when serum is separated from the clotting blood. This hypothesis continues to be conjectural.

Weech, Geottsch and Reeves (62) in 1933 while doing plasmapheresis experiments in dogs were able to produce a normal state in their animals by administering transfusion of normal dog serum.

Elliott (16) in 1936 suggested the use of untyped serum and plasma for the treatment of surgical, obstetrical or traumatic shock where transfusions were indicated. He rationalized that the need for replacing the lost blood volume was more important than the red blood cells, as the maintenance of osmotic pressure is a function of the plasma proteins. Elliott also propounded the idea

that liquid plasma could be stored for long periods without deterioration. The findings of other investigators have supported his contentions.

Fantus (22) in 1937, advocated the use of normal human serum because of its therapeutic and natural immunizing properties. He states that in shock without hemorrhage and in burns that the intravenous injection of blood serum is much more rational than that of blood because these patients usually have an excess of red blood cells per cubic millimeter.

Mahoney, (40) in 1938, recorded encouraging results with preserved plasma in the treatment of experimental and clinical shock.

McClure (38) in 1939, working separately obtained good results with plasma in burn cases. Tatum, Elliott and Nesset, (55) in 1939, suggested a technique for the preparation of whole blood substitutes in war conditions. Plasma was recommended as "an ideal substitute for whole blood in the emergency treatment of shock and hemorrhage from war wounds". They outlined the technique of collecting blood in a vacuum bottle, centrifuging the blood and then aspirating the supernatant plasma into a second vacuum bottle for storage.

In 1940 Elliott, Busby and Tatum (18) recommended the use of dilute, preserved, liquid plasma. The same

year Strumia (53) advocated citrated blood plasma without cross-matching for the treatment of burns and shock.

Thalhimer (56) reported favorably on the use of convalescent serum for administering antibodies.

Best and Solandt (4) discussing their work on experimental shock reported encouraging evidence in favor of using plasma and serum in preventing shock.

Levinson, Neuwelt and Necheles (36) have shown the value of serum in the treatment of posthemorrhagic shock in experimental animals.

Kendrick, (35) 1941, advocated the use for military purposes of concentrated and normal dilutions of plasma for the prevention and treatment of shock in the combat zone.

Kekwick and Whitby (34) 1941, after using it for the treatment of shock and hemorrhage in air raid casualties in England, concluded that plasma and blood are equally effective in restoring blood volume in injuries of this type.

The previous remarks have been confined to liquid plasma. With the development of drying equipment for desiccating biologicals, dried plasma has become a reality. Serum was dried successfully as early as 1896 by Martin (42) who described a simple method of preserving serum by evaporating it to near dryness under a partial

vacuum at 40° C. Since Edwards and Kay and Davie, (14) and others, have prepared dried serum and plasma by distillation or pervaporization from the fluid state.

In 1935 Elser, Thomas and Steffen (21) and later Flosdorf and Mudd (35) recommended preservation of serum in the "lypohile" form.

In 1940, there appeared in the literature a description of the Desivac drying machine, also developed by Flosdorf, Stokes and Mudd (24). In this process the moisture is removed under vacuum by an oil centrifuge pump. In 1940, Hill and Pfeiffer (31) described the Adtevac process for drying plasma. The efficiency of this system is dependent upon the ability of silica-gel to absorb large quantities of water vacuum.

III

RATIONALE OF PLASMA TRANSFUSION

Studies of Pathology of shock have shown that although there may have been a considerable loss of blood, and although the patient appears to be very pale, there is in actual fact a concentration of the red blood cells in the blood. The capillary red blood cell count may be as high as 8,000,000, but the circulating volume of blood is diminished. In the case of severe burns this

state of affirs is even more accentuated; the red cell count may be higher still while the patient is positively dehydrated. In these cases it is obvious that there is a loss of fluid from the circulation and the essential elements to be replenished is not the red cell content of the blood, but the plasma. The most important constituent of the plasma is its proteins, the osmotic pressure of which is the main factor in maintaining the circulatory volume. The administration of fluids such as saline to these cases merely dilutes the remaining protein; saline soon passes out into the tissues or is excreted by the kidneys. If, on the other hand, plasma proteins are present in the fluid administered intravenously, then they will tend to keep it in circulation. The administration of red blood cells to such cases in the acute phase of shock tends merely to increase the hemoconcentration and the viscosity of the blood, which is apt to depress the patients vital reserve still further. Obviously what is needed in the circulation is plasma; what is not needed, indeed, what is definitely harmful, are red cells. Here, therefor we have the rationale of plasma transfusion.

IV
CONSTITUENTS OF PLASMA & SERUM

Plasma & serum differ slightly in composition. Plasma is the supernatant fluid which separates from the cellular elements when an anti-coagulant is added to blood. Serum is the liquid portion of blood that separates when blood clots. Plasma therefore, is the liquid portion of the blood separated without clotting and may be regarded as a liquid solution of albumen, globulin and fibrinogen. Other stabile components of plasma and serum are complement, Prothrombin and antibodies of Scarlet Fever, Measles, Mumps, Pertussis and other infections.

The only difference in composition between serum and plasma is the the latter contains fibrinogen, the former does not.

V
AVAILABLE STATES OF PLASMA AND SERUM

Serum and plasma are now being prepared and dispensed in various forms. Serum can be give in a liquid state or it can be regenerated from the dried state & injected concentrated or normally diluted. Plasma can also be frozen immediately after processing and preserved in this state indefinitely. It may be dried or

thawed rapidly and administered. When plasma or serum is reactivated, Pyrogen-free distilled water is used as the dilvent. To make four times concentrated plasma, only one-fourth of the original water content is added to the dry material. One of the main advantages of plasma and serum is that they can be preserved for long periods with very little change in the composition. Properly prepared liquid plasma can be given safely after six month's storage without refrigeration. Dried plasma, sealed under glass with a partial vacuum can be preserved for at least five years. In the frozen state plasma and serum can be preserved indefinitely without alteration of their constituents.

A. Liquid Plasma

The primary advantage of liquid plasma is that it is immediately available for use.

The main disadvantages are: (a) Loss of prothrombin and complement on storage. (b) Tendency to fibrin formation on storage. Plasma proteins show definite changes after one year. (c) Liquid plasma serves as a much better culture medium than desiccated or frozen plasma.

B. Frozen Plasma

Frozen plasma offers many advantages over liquid

plasma inasmuch as the full prothrombin, complement and fibrinogen can be retained for a long period of time. It offers practically the same advantages of properly prepared desiccated human plasma. This method offers the ideal method of storing convalescent human serum and plasma. The main dis-advantages are: (a) The need of constant low temperature refrigeration and the necessity of restoring the plasma to the liquid state at or near 37° C. It is quite as satisfactory as desiccated plasma in any hospital having a refrigeration unit that maintains a temperature at or near 20° C.

C. Desiccated Human Plasma

There are numerous methods for desiccating human plasma and no attempt will be made to evaluate these methods. A few of the mthods of desiccation are relatively simple, while othersare complicated and require expensive apparatus.

A satisfactory desiccated plasma should have a moisture content of less than 1%, free from fusion and have a solubility of less than 5 minutes when restored to the original volume. Properly prepared dried plasma retains most of its complement, prothrombin and fibrinogen, and if properly bottled it can be stored at room temperature for several years with very little

deterioration of any of the normal constituents. The main disadvantages of this type of plasma is the necessity of having sterile, pyrogen-free water on hand for restoration to the liquid state.

D. Lyophile Serum

Bond & Wright, (8) suggested the use of lyophile serum which has been preserved unaltered. When this substance has been redissolived and injected intravenously in dogs, in which the blood pressure was severly reduced by trauma to gut or extremity or by hemorrhage, the blood pressure was raised and maintained for at least several hours.

The immediate availability of lypohile serum, its theoretical suitability & its action upon shocked animals suggest its use as a valuable treatment for clinical shock & hemorrhage.

VI

INDICATIONS

After blood groups were known to exist, it was possible to transfuse blood only with suitable laboratory facilities and donors. Whole blood transfusions are thus impossible under war conditions where they are needed.

After it was known that blood could be stored for comparatively short periods, the difficulties were reduced somewhat, but laboratory facilities were still necessary just before using the blood.

Blood serum or plasma, was found to be an ideal substitute, and in some cases more effective than whole blood. The mechanism of shock following hemorrhage is different from shock following trauma. In shock from trauma, there is a loss of plasma into the tissues and a concentration of red cells in the capillaries; whereas in shock from hemorrhage, there is a loss in plasma and cells from the blood. In both cases the loss in plasma is responsible for the drop in blood pressure and the concomitant shock. In treating such cases, plasma is very effective until red cell replacements, following hemorrhages, are available.

Plasma has certain distinct advantages in time of emergency for three reasons: (1) Plasma can be stored for a relatively long period of time, and (2) Plasma can be transported long distances safely, and (3) it can be transfused without typing or cross agglutination as has been shown by numerous transfusions with and without incompatible agglutinins in the whole blood. No difficulties have been encountered by the use of blood from so-called "dangerous universal donors".

By the use of sealed Vacuum Transfusion Sets during a time of war, blood can be drawn, the plasma prepared and sent to any locality for use in emergencies. Employing a stainless stell mesh filter within a glass unit to determine the rate of administration and a unit containing physiological solium chloride a plasma infusion may be carried out in any locality.

1. Plasma should be an ideal substitute for whole blood in emergency treatment of shock and hemorrhage from war wounds.

2. Since transportation will not effect plasma, it can be prepared where the source of blood supply is great, stored for long periods of time, and sent to the point where it is most needed.

3. No laboratory typing and cross-agglutinating are necessary.

4. A technique for the safe aseptic preparation is outlined. (55)

Restoration of circulating blood volume is the essential aim of the treatment of shock, regardless of its cause, whether hematogenic, neurogenic, vasogenic or strictly post hemorrhagic. There is a general agreement with regard to the general mechanism of shock, namely a disparity in blood volume relative to vascular

capacity.

Blalock (6) & Moon (45) particularly have emphasized this point & stressed the importance of plasma loss from damaged capillaries. A vicious cycle tends to be set up, with progressive vascular damage resulting from anoxemia. The more profound the shock, the more urgent is the necessity for a speedy reversal of this mechanism before irreparable damage occurs.

Hill & Pfeiffer (31) showed that concentrated plasma appears ideal for this purpose for several reasons. Firts, large amounts of protein can be more speedily placed in the circulation. Furthermore, hypertonic plasma tends to effect an immediate reversal of the abnormal physiologic changes of shock. Blood volume is built up by immediate withdrawal from the tissues of fluid previously lost from the blood stream. Finally it seems probable that concentrated plasma has a direct stimulating effect on vascular tone & permeability. The second groups of indications for plasma therapy is concerned with the control of plasma protein levels, a problem of increasing importance in modern surgery. The quantity of protein required to combat hypoproteinemia make it highly desirable to give this type of feeding in concentrated form. By this method blood proteins

levels can be rapidly raised & sustained when suitable amount are given.

It was stated that prolonged preservation of antibodies, prothrombin & complements in plasma can be accomplished only by desiccation from the frozen state. The application of these facts to the treatment of infections by concentrated plasma involves special hypertonic effects required to accomplish substantial shifts of fluid. Reduction ofincreased intercranial pressure by concentrated plasma as reported by Hughes, Mudd & Strecker (33) is an example of such uses. For these purposes hypertonic plasma protein are superior because of the prolonged osmotic effect.

Concentrated plasma is prepared by redissolving the dry lyophilic form obtained through disiccation from the frozen state. The plasma prepared in this manner exhibits in a greater degree not only all the desirable properties claimed for whole plasma but also additional advantages both technical & therapeutic. The technical advantages of desiccation & concentration relating to storage, transportation, simplicity & speed of administration are discussed in a previous article.(31)

The importance of these prodical technical factors should not minimized particularly in connection with

military requirements.

However, the therapeutic advantages are even more significant & can be attributed chiefly to the control of osmotic forces made possible by rise of concentration up to four or five times normal. These advantages of concentrated plasma suggest three principal groups of indications; first, regulation of blood volume; second, control of plasma protein levels, and third, special adjustments of fluid balance when marked hypertonic effects are essential.

On the basis of clinical results in 45 closely followed cases of shock, intravenous hypertonic plasma is advocated as a treatment of choice in shock.

The safety of this form of therapy is reflect in the low febrile reaction rate of 1.003 per cent among 299 administration.of concentrated plasma.

In a series of eleven dogs disruption of the wound, or a failure of the wound to heal during hypo-proteinemic states was observed eight times, an incidence of 72 per cent. Tissue was removed from four of the dogs for study at intervals of seven days. In others serious infections occurred following eviscerations, resulting in badly infected wounds or in peritonitis & death.

At the time that the incisions were made the

tissues were paler than noraml & frequently looked as though a local anaesthetic had been recently injected. At the time of the first & second biopsy specimens were taken the wounds were found in four instances not to be healed, although when silk sutures were used they were frequently holding the edges together. In cutting across a wound to obtain a biopsy specimen, the tissue was found to be unhealthy looking, and serous fluid could easily be expressed from surfaces of the wound even as late as fourteen days after the abdominal incision was made. The tissues around the site of the incision were edematous, glistening and pale, and the bleeding was not as great as would be expected from an incision at right angles to the original incision. There was no apparent attempt at union of the wound. A serous material was interposed, keeping the surfaces bathed in a solvent which prevented even the sticky adherence found in very early sterile wounds.

In the study of sections taken seven & fourteen days after operation, there was little difference, except that the tissue edema was even more prominent. Fibroblastic proliferation was found only occasionally in the seven day section, indicating a marked delay

in fibroblastic regeneration. In the fourteen day sections fibroblasts were observed but in greatly decreased numbers. The histologic picture was that of marked delay in tissue repair.

The part which plasma proteins play in holding fluid in blood vessels can not be overlooked. As the colloid osmotic pressure of the plasma proteins is reduced from its normal level, fluid leaves the vessels and passes into the intercellular spaces. The addition of large amounts of solution of Sodium Chloride intensifies the resulting edema. Those several factors work hand in hand to produce a condition which is inimical to satisfactory repair of the wound. (58)

Experiments were performed on dogs exhibiting serum albumen deficits produced by protein starvation, which indicates that transfusion with normal dog serum is followed by an immediate rise in concentration of serum albumen and usually a fall in the concentration of plasma globulin when the results are expressed as total circulating protein, rather than on terms of concentration, it is seen that both albumen and globulin are increased by the procedure. (62)

Thompson, etal. (57) showed the relationship between hypo-porteinemia and disruption of wounds by

demonstrating that delay in healing wounds in hypo-proteinemia dogs may be prevented by promptly restoring the serum protein to a normal level after laporatomy and maintaining this level during the periof of healing. They used the plasma removed by plasmaphoresis, which had been lypophilized and kept in a dehydrated state until just prior to injection.

In three dogs subject to bilateral laporatomy during the hypo-proteinemic state, disruptio of the wound or failure to heal was not observed when the hypo-proteinemia was controlled, after abdominal incision, by intravenous infusion of lypohile plasma.

At the time the incisions were made the tissues were paler than noraml and looked as though a local anaesthetic had recently been injected. The wounds at the time of the first biopsy after the abdominal incisions were somewhat drier than at the first operation, but were still moist. At the end of seven days the serum proteins were normal in each instance. The wounds appeared grossly to be healing normally on the fourteenth post operative day, at the time of the second biopsy, the wounds appeared grossly to be normally healed. The wounds at the time of the first and second biopsies had no similarity to those observed in

hypo-proteinemic dogs except moderate moistness which was observed at the first biopsy. Considerable fibroplasia was grossly evident seven days after the abdominal incisions.

They concluded that retardation in healing of wound associated with hypo-proteinemia in dogs may be averted by restoration of the serum protein to normal levels immediately after operation. (57)

VII

MECHANISM OF SHOCK

Circulatory failure of capillary origin produces a clinical syndrome which is highly characteristic. This is accompanied by an equally characteristic group physiologic and biochemical features. These constitute the clinical syndrome of shock.

The gross and microscopic changes seen post mortem are equally significant. These consist of capillary damage, such as dilatation, stasis, petechial hemorrhages, edema and effusions, present in extensive vesceral areas. These features are etiologically related to the mechanism by which capillary deficiency of capillary origin developes.

Hemoconcentration is a highly valuable clinical sign indicating the early stages of this condition. It occurs before other signs of circulatory deficiencies are manifest.

The mechanism of this type of circulatory failure includes the reciprocal effects of two major factors- capillary atony and tissue anoxia. Either of these factors will presently cause the development of the o other. This reciprocal action gives the circulatory deficiency a self-perpetuating quality deficiency a which tends toward a irreversible condition.

Few conditions of disease present a more characteristic group of clinical features, physiologic abnormalities and morphologic visceral changes. This snydrome, if caused by a single etiologic agent, would constitute an entity among diseases. But the origin of this syndrome is highly diversified .

It may originate from numerous and varied agents and conditions which may injure directly the capillary endothilium, from loss of blood or fluid sufficient to produce systemic anoxia from agents or conditions which reduce the volume flow of blood below physiologic limits, from asphyxia of external or internal origin, or from various combinations of the conditions mentioned.

Efforts to combat this type of circulatory deficiency will be directed toward the recognition and removal of the cause and toward interrupting the operation of the vicious circle. If the former cannot be accomplished the latter will be ineffective.

Until someagent is found which will prevent or relieve capillary atony, efforts to interrupt the circle should be directed toward the restoration of blood volume and toward relieving tissue anoxia. The irreversibility requires early recognition and action. Hemoconcentration is recommended for recognizing the early stages of circulatory deficiency of this type.

In view of this premise it appears obvious that the ideal therapeutic agent would be one enabling the physician to increase rapidly and permanently the patients blood volume. Strumia (54) etal. concluded that intravenous administration of citrated blood plasma has proven to be an ideal means of restoring an adequate blood circulation in patients suffering from secondary shock, rapidly relieving the clinical manifestations. The advantages offered by citrated blood plasma are that (1) It can be readily prepared and safely transported. (2) It can be stored for an indefinite period of time. (3) It is entirely safe and free from re-

actions. (4) It can be used in large and repeated doses. (5) It is ready for instant use. (6) It does not add to concentration of crythrocytes if this condition is present. (45)

VIII

PLASMA TRANSFUSION IN SHOCK

The term traumatic shock, indicates a state of circulatory collapse which follows injury, and is characterized by a decrease in the circulating blood volume, Mahoney (40). This type of shock differs from that due to acute hemorrhage insofar as fluid loss in the latter is due to loss of whole blood, while in traumatic shock, fluid loss is due primarily to diminution of the blood plasma, and only to a minor degree to loss of whole blood. The transfusion of whole blood has been found to be the most satisfactory method of restoring the plasma proteins, the blood voluem, and the cells in cases of shock due to hemorrhage. In cases of traumatic shock, however, where there has been no loss of cells and the blood is already concentrated by loss of plasma, the transfusion of whole blood adds to the already increased viscosity by increasing the number of red cells. The use of transfusions of blood

plasma in such cases, therefore, seems more advisable.

The author produced shock in dogs experimentally by cooling the peritoneal cavity. It was then demonstrated that in these animals there was an excessive loss of plasma from the circulating blood, and that albumin constituted the major portion of this loss.

Preserved plasma when compared with whole blood, saline and acacia in the treatment of this type of shock was found to be the most efficient agent in restoring the normal blood pressure. In another set of experiments, shock was produced by traumatization of one extremity of the experimental animal. This type of shock was associated with a loss of the red cells and plasma and was more nearly comparable to the shock resulting from hemorrhage. Treatment of this type of shock with preserved plasma was less effective than for the type associated with loss of plasma alone. (40)

It seems that any agent that would increase rapidly and permanently the blood volume would be satisfactory. Recently whole blood transfusions have seemed most effective. Physiological saline and dextrose solutions do not produce a permanent increase in blood voluem. Acacia solution, although more effective than a physiologic solution of sodium chloride in maintain-

ing this circulating volume, is often followed by severe reactions.

Whole blood is not satisfactory because, (1) the time necessary to make it ready for the transfusion, is valuable, and (2) the undesirable addition of red cells to the already concentrated blood. Preserved citrated blood promised to remedy the first objection, but the period of storage was limited and time was necessary for proper crossmatching. The use of preserved blood was further limited by the fact that it cannot be transported because mechanical agitation breaks down the red cells. Also post transfusion reactions are common when citrated blood is administered too fast.

Lypohiled serum according to Bond and Wright, is capable of raising and maintaining blood pressure for several hours. Numerous other workers mention the use of serum and plasma, but this paper points out the advantages of plasma over serum which may be summarized briefly: (1) the greater yield of the fluid portion when citrated plasma is separated by centrifugation, and (2) the all important freedom from reactions which are often severe when serum is employed intravenously. In ten cases cited, citrated plasma was used exclusively in the treatment of shock with ideal results.

Plasma may be given in large enough amounts to entirely relieve the symptoms of shock, the average amount being 500 c.c.'s. It may be given at the rate of 10 c.c.'s per minute. It is preferable to use the plasma diluted with an equal amount of saline dextrose solution, although this is not essential. The heating of plasma in any way is to be carefully avoided. The administration of cold plasma does not cause any reaction.

Plasma appears to be the ideal material for the reestablishment of proper circulation in secondary shock. Becauseof the protein content and the consequent high colloidal osmotic pressure, plasma does not leave the circulation system as do crystalloids.

Citrated blood plasma is readily obtained from citrated blood with a high yield; it may be pooled and stored indefinitely after serologic tests have been carried out. It is entirely safe and free from reactions and may be used in large and repeated doses. Plasma so prepared is ready for instant use and does not add to the concentration of erythrocytes, if this condition exists. (54)

In secondary, or hemotogenic shock, associated with reduced blood volume, blood and blood plasma are of great value in treatment. Salt solution infusions

are unsatisfactory because not only does the salt solution leave the circulation, but blood proteins are carried out also when plasma, blood, or serum is used in the presence of increased capillary permeability, such a marked out-pouring of blood proteins does not occur. In discussing the use of plasma, Blalock states that although hemo-concentration is usually present in shock, the bad effects of hemoconcentration have been over-estimated, especially of blood volume is maintained. A given quantity of plasma causes a greater increase in osmotic pressure than does an equal quantity of whole blood. Plasma can be stored more easily than can whole blood and the danger of reaction is less, especially if the plasma is pooled in order to decrease the concentration of agglutinins.(7)

In surgical shock there is tissue damage with loss of plasma at the site of injury, secondary peripheral vascular failure and discrepancy between the size of the vascular bed and the volume of circulating blood. The capillaries become dilated, the flow of blood is retarded and the tissues become poorly oxygenated. As a result of the anoxia, the cells are injured and undergo functional and degenerative changes. The capillaries become permeable to proteins and the blood proteins

escape into the tissues carrying with them fluids with resulting edema. Loss of proteins lowers the osmotic pressure of blood causing edema but this is not massive and clinically manifested until the protein depletion is less than 5 grs. per 100 c.c. As the fluid leaves the blood vessels, the cells left behind become more concentrated (hemo concentration) and the flow of blood becomes thick and viscid, thus slowing the flow of blood. The cells themselves become edematous and swollen which further interfers with circulation.

Blood plasma is useful in the treatment of shock because it supplies needed proteins and restores blood volume. The proteins in the plasma pull fluid back from the tissues and from the red and white cells and holds this fluid in circulation and oxygenation becomes more adequate, red cells circulate better through the lungs and the vicous circle is broke. (13)

The early replacement of the lost fluid is by far the most important form of therapy known to prevent shock. Saline is not retained in the circulation for any length of time, and the elevation of blood pressure is only temporary. It not only is lost from the circulation, but it carries some of the protein molecules from the blood stream into the tissues with it. It is

advisable to use acacia only when blood and other substitutes are not available. During the last three years the use of plasma and serum as blood substitutes has been investigated. It is clear that ther is an adequate replacement of the lost fluid in shock by plasma, when the alterations in physiology are considered.

Plasma is safer and better to use than serum, because its yield from whole blood is greater and it is entirely free from reactions. Lyophiled plasma reduces the bulk of liquid plasma, although regeneration by the addition of distilled water is necessary. The use of plasma as far forward as the Battalion Aid Station, will depend largely on the plan of combat and its development. Therefore, it may be conceivable that instructions for the use of plasma be included in the Medical Field Order. (35)

If the problem is merely to restore fluid and electrolytes to a dehydrated patient with a normal amount of plasma protein, and with uninjured capillaries, the treatment is relatively simple. On the other hand, it is far more difficult to restore and maintain an effective circulating volume of blood in a patient whose capillaries have allowed and are continuing to allow, a loss of all the plasma elements including

plasma proteins. Fluids and electrolytes are necessary but must be administered according to the needs of the patient.

In cases of increased capillary permeability, the intravenous administration of aqueous solutions is of no benefit. The aqueous solutions dilute the plasma chloride in the blood and bring them to a concentration which makes it impossible to hold the administered fluid in the blood stream. Tissue edema develops, and the result is extensive capillary damage, so that protein escapes with fluid. Frequent measurements of hematocrit of hemoglobin, and plasma protein, afford the best quide as to the disposal being made of fluid administered.

Transfusion of blood plasma is probably the method of choice for restoration of plasma volume. The use of plasma, rather than whole blood, avoids further burdening of the circulation with cellular elements which are already present in high concentration. Volume for volume, plasma transfusion introduce protein approximately twice as fast as when whole blood is given. The value anc convenience of having available a "Plasma Bank" can hardly be over-estimated in the treatment of patient with capillary injur. (44)

Mahoney, Etal. (41) observed that plasma is essentially comparable to whole blood in the treatment of shock resulting from hemorrhage, trauma, or burns. It is valuable in combating certain types of hypoproteinemia, in restoring the water balance of dehydrated patients, in preventing operative shock, in checking certain hemorrhagic tendencies and in a variety of other conditions demanding a readily available supply of protein.

The therapeutic effacacy, the ease of preservation and transportation make plasma or serum the ideal substitute for whole blood in times of emergency.

These authors concluded that: (1) Pooled blood plasma may be injected intravenouly without regard to blood type. (2) The incidence of reactions to plasma transfusion is 3.5 per cent. None of the reactions have been serious. (3) Plasma is an effective substitute for whole blood in treating peripheral circulatory failure due to trauma, operations, burns and hemorrhage. (4) Plasma is effective in treating temporary hypo-proteinemia, especially in the surgical patient. (5) Dried plasma retains properties which are effective in treating hemophilia. (6) Present experience indicates that plasma, dried within a few hours after removal from the donor, is effective in treat-

ing hemorrhagic disease of the new-born. (41)

IX

POST-OPERATIVE COMPLICATIONS

Most patients subjected to operation on the various parts of the gastro-intestinal tract have had appreciable hindrance to optimun nutrition before surgical intervention was undertaken. The exhaustion of stored substances together with the inability to feed in an adequate or natural manner during the immediate post-operative period, may result in Anemia, Avitaminosis, weight loss and protein deficiency.

Continuous drainage from the gastro-intestinal tract by vomiting, diarrhea etc., depletes the body sodium and chlorides in variable amounts. The patient must be watched for indications of acidosis or alkalosis, as evidenced by the carbon dioxide combining power of the blood and blood chloride level.

If the patient has stores of sugar, salt, iron and fluids laid up before operation, upon which to draw, the post operative period will not be difficult to manage. In any case, prompt administration of whole blood or plasma transfusion together with glucose, salt as re-

quired will supply deficiencies.

X

USE OF PLASMA IN POST-OPERATIVE COMPLICATIONS

Numerous post-operative complications are in part due to low plasma proteins and can be helped or prevented by plasma transfusion alone. It has been clearly shown that liver injury and functional failure are less likely to occur following operations if the proteins are adequate. When the plasma proteins are low there is tissue edema and interference with normal intestional motility and proper gastric emptying, hence the greater liklihood of vomiting, intestinal stasis and improper functioning following abdominal surgery. In experimental animals and in patients with low proteins, the suture lin in intestional anastomosis becomes more edematous than normal and remain so for a longer period of time, thus producing symptoms of non-functioning lumen and intestinal obstruction. Wounds of all sorts heal more slowly and sutures are more likely to break down when the plasma proteins are decreased. Pulmonary edema is more likely to occur when the proteins are inadequate. Intravenous

plasma is therefore essential in the pre-and post-operative care of surgical patients.

XI

PLASMA TRANSFUSION IN EXPERIMENTAL INTESTINAL OBSTRUCTION

Fine, observed that the plasma lost by intestinal obstruction is sufficient to produce death. Most of the plasma loss is due to distention alone. Some loss however, is due to dehydration. Previous studies have shown that loss of blood, fluid and electrolytes into the intestinal lumen, bowel wall and peritoneal cavity was not responsible for the plasma loss or for the rapid death from obstruction with distention. The one uniform finding, constituting an explanation for the quicker death of the distended animals was a progressive and extensive loss of blood plasma.

It is believed that the distention produces plasma loss into the interstitial spaces of pelvis and lower limbs because of the impeded venous return from these areas. This paper describes the results of experiment to explain the effect of plasma transfusion to replace this plasma loss.

Using dogs, the normal plasma and whole blood volume were determined under anesthesia. After twenty-four hours of starvation, the pylorus was ligated and the ileocecal valve was divided, its distal end inverted and a glass canula tied to its proximal end and connected to a Peruse pressure bottle. The entire small intestine was inflated with air at a clinical and experimental level until death occured.

Plasma diluted to two or three times its volume with saline was administered at a rate of five to eight drops per minute. To determine the specific volume of plasma and whole blood, physiologic saline with and without acacia was given.

The intravenous injection of plasma in amount adequate to replace that loss as a result of obstruction and distention of the empty small intestine, offers a protective influence sufficient to markedly prolong the life of the animal.

The intravenous injection of physiologic saline in amount sufficient, or more than sufficient to replace fluid lost under the conditions of the experimental technique, confers no noticeable benefit.

Loss of plasma continues so long as distention continues in the obstructed small intestine of the dog.

The extent of this loss, if uncompensated, is sufficient in itself to cause death, and is of primary importance in the pathologic physiology of intestinal obstruction. (23)

XII

PLASMA TRANSFUSION IN SHOCK DUE TO BURNS

Subsequent to a burn the capillaries in the injured areas dilate. The circulation stagnates, the blood plasma escapes through these injured capillaries into tissue spaces. Intravenous fluids merely wash out into the tissue spaces. This is true circulatory shock from the mechanical loss of fluids, are reported by Blalock. (6)

Because added fluids would add to the water logging process, it is logical to assume that plasma is the treatment of choice in extensive burns and that systemic treatment is as important, or more so than local treatment. (60)

In these studies great clinical improvement followed infusion of dilute plasma and was accompanied by a rise in plasma volume in those cases in which observations of blood volume were possible. The results with four times normal serum were much less favorable. (5)

In cases of severe burns it is just as important to treat the patient, as it is to treat the wounds. Supportive measures should include repeated sedation for pain and restlessness, oxygen therapy when indicated, external heat should be applied, restoration of fluid balance by oral, rectal, interstitial and intravenous use of 5% dextrose and physiologic solution of sodium chloride. Blood plasma infusions should be given. Whloe blood should be used only when the blood concentration is not normal, as indicated by repeated hemoglobin or hematocrit determinations. When hemoglobin values of more than 15.6 gr. are obtained, plasma transfusions should be given.

Local treatment of a burn should be the same as for any extensive surgical wound. (38)

It has been known for some time that a decrease in the fluid portion of the blood, anhydremia, oligemia, or hemoconcentration, is commonly associated with severe burns. Studies have shown that the capillaires in the burned area are readily permeable to methylene blue and trypan blue, and that in a burn of one-sixth of the body surface, the local edema fluid was equal to 70% of the total blood volume, and finally that the composition of the local edema fluid closely resembles that of blood

plasma. In dogs it has been demonstrated that there is a considerable reduction in "bleeding volume" and hence in blood volume, indicated a fluid shift to the burned area. Other workers found in burned dogs a 21% to 60% reduction in plasma volume. This fluid inbalance is primarily an abnormal distribution or shift of fluid, rather than an external loss.

Consequently, this fluid lost from the vascular compartment to the tissues would best be replaced by returning the lost plasma protein. When the external loss of fluids is not great, the need for water and electrolytes is moderate only, as the excess fluid in tissues should be available when the plasma osmotic pressure is restored to a normal level. The administration of excessive amount of physiologic saline solution without plasma protein only increases the edema already present, and must be given in dangerously large amounts to have any signigicant effect on the plasma volume. The administration of water without salts may produce water intoxication.

Cases of moderately severe burns are presented, and the results are in accord with the view that fluid inbalance is primarily due to altered permeability, with a shift of fluid and protein into the tissues rather than an external loss. Evidence is presented that the loss of

plasma protein continues until the thirty-first to fortieth hour. During this time excessive hemoconcentration may be prevented by small repeated transfusions of plasma. After the fortieth hour the capillaries have regained their impermeability to protein and the deficit of plasma protein may be corrected by one large plasma transfusion. (15)

Loss of protein is clearly an important and serious effect of severe cutaneous burns. This loss affects not only the tissue proteins but plasma proteins. It seems likely that many, if not all, of the general manifestations of severe cutaneous burns are connected with this loss. As far as plasma is concerned it is obvious that fluid containing only dextrose or saline solution alone will not in itself replace this loss because of the essential need for plasma protein. This need is due to the importance of maintaining osmotic pressure of the circulating blood. Fluid without colloid properties when injected intravenously soon escapes from the blood bed and fails to relieve the essential hemoconcentration.

Both experimental and clinical observations confirm the importance of fluid inbalance in burns and indicate that it commences and, in the case of severe burns, may

reach a marked degree within the first few hours.

The mechanism responsible may be briefly outlined as follows: As a consequence of capillary stasis and altered permeability in the burned area, the passage of plasma protein occurs across the capillary membrane, with corresponding disturbance of osmotic pressure relationships, leading to increase in the tissue fluids and decrease in the plasma volume. The fluid inbalance thus produced is not primarily an external loss, but a shift or abnormal distribution. (15)

Experimental and clinical studies indicate that the loss of plasma protein continues until the thirty-first to fortieth hour after the injury and thus suggest the advisability of small repeated plasma transfusion during this period.

That plasma or serum transfusion are efficacious in burn shock has now been amply demonstrated, among the recent reports being those of Elkinton, (15) Black, (5) and Kendrick. (35)

Black, (5) reports the period during which patients with burns are in jeopardy from shock to be from forty-eight to seventy-two hours after the injury and comments that, in the absence of any direct method for improving capillary tone, the object of treatment is, replacement

of the fluid and protein which have been lost, to maintain an adequate blood volume.

As he also states, the translation into clinical idiom of the indications for plasma or serum transfusion is made difficult by the inconstant relation between the fall in blood volume, which is the fundamental indication for plasma or serum therapy, and the usual clinical data such as the blood pressure and pulse rate. For, while any fall in blood pressure coupled with an increase in the pulse rate above 100 is a clear indication for serum or plasma therapy, certain cases may be in the early stages of progressive shock and yet show no alteration in blood pressure and no great changes in the pulse. In such cases, by the time significant changes have occurred in the blood pressure, recovery may be impossible or extremely large doses of plasma may be required, whereas, administered earlier, smaller doses would have sufficed.

XIII

DOSAGE OF PLASMA OR SERUM

The cardinal principle in the use of plasma or serum is to administer an adequate amount early. The more recent reports on the treatment of shock show that the injection of relatively large quantities of plasma or serum is essential to restore normal circulating blood volume. It has been demonstrated both experimentally and clinically that approximately 25% (1 liter in man) of the plasma volume is lost in mild shock. In severe shock this loss may be doubled. It becomes apparent then that the injection of small amounts (250-500 c.c.) of plasma are entirely inadequate in restoring the depleted plasma volume. Kewick, (34) etal, have shown that it is necessary to give to the severly injured 1-2 liters of plasma or serum in order to elevate the blood pressure to a physiologic level. There is a direct ratio between the amount of plasma needed and the elapsed time after the injury. If the plasma is administered early the quantity required is greatly reduced. Better clinical results may be expected by giving 500 c.c. of plasma or serum within the first two hours than by giving large amount several hours after injury. In the treatment of burns involving 1/6 to 1/3 of the total body

area it is essential that large amounts of plasma be administered. During the first 24 - 48 hours it may be necessary and frequently is imperative that 3 - 6 liters of normal plasma be used. This will have to be supplemented by additional amounts of 1 - 3 liters daily. The amount and length of time that will be required may be ascertained by red blood cell counts, hemoglobin, hematocrit and serum protein determinations.

The amount of plasma to give in cases of shock is difficult to state. It has been found that the general condition of the patient and his blood pressure are more reliable in telling how much plasma to give than are laboratory tests. When the blood pressure is below 80 Systolic and below 40 Diastolic, there is circulatory failure, and emergency measures are in order. Five hundred c.c. of plasma can be calculated to raise the blood pressure 10 - 20 mm of Hg. The tendency is to five too little rather than too much. The patient may need liters of plasma to compensate for protein losses and to re-establish normal circulation. (13)

XIV

PLASMA VS. SERUM TRANSFUSION

While there is no attempt to prove that plasma is more beneficial than serum. The advantages of each will be presented. Both plasma and serum are human colloidal protein-containing fluids, and both are thus in every way suited for restoration of the fluid loss in shock. Discussion as to their relative merits has centered largely upon the frequency of reactions encountered after one or the other. Strumia, (53) advocates plasma rather than serum transfusion because of the possibility of reactions following the use of serum, which reactions, he believes, are probably due to fibrin precipitation during the separation of the serum by clotting. A further advantage of plasma, in his opinion, is that it may be given safely when five times concentrated. Levinson, (36) however, in a discussion very properly comments that properly prepared serum is not toxic per se and that many of the reactions reported after serum transfusion are related to technical imperfections in its preparation. He prefers serum because it does not contain citrate and because fibrin precipitates do not occur during storage.

It may not be amiss to recall that the early concept of sodium citrate as an important factor in the pro-

duction of transfusion reactions has been largely, if not entirely, overthrown by accumulated experience and that, in the proportions present under all average circumstances (0.35 per cent), its administration has been shown to be entirely safe and without relation to reactions.

Levinson, (36) in an experimental study of serum transfusion in dogs, also reports, however, an incidence of "serum reactions" of about 25 per cent described as of somewhat unusual character, never repeated upon subsequent transfusion of the same serum, and for which no common causative factor was discovered. In a further report by the same investigator (36) of human serum transfusion of from 500 to 1,400 c.c., only one minor reaction was encountered (forty-seven cases). Emphasis is again laid upon the necessity for meticulous care in the preparation of the serum as an effectual preventive against reactions.

Levinson and his associates base their preference for serum rather than plasma largely upon the fact that in the storage of citrated plasma the gradual appearance of fibrin veils and granular precipitates necessitates clearing by centrifugation or filtration before administration. Serum, on the other hand, after its preparation

and clarification, remains clear indefinitely.

Best and Solandt, (4) emphasize that both serum and plasma are identical in their physiologic action and are thus therapeutically interchangeable. Thus, any preference for one or the other arises largely from circumstances pertaining to their collection and preparation.

Strumia and McGraw, (52) list as particular advantages of plasma over whole blood freedom from reactions except for relatively rare instances of mild urticaria; plasma may be administered in large amounts and in repeated doses; if desired, plasma may be concentrated; and, finally, plasma transfusions do not increase hemoconcentration.

In addition, plasma may be stored longer than blood, is more easily transported because refrigeration is not essential, need not be typed, and when properly prepared does not require filtration because of fibrin precipitation.

The preference of these authors for plasma over serum is largely based upon the greater yield if centrifugation is employed: the coordination of plasma production with the functioning of a blood bank; and the absence of other than occasional mild urticarial reactions.

A report of forty-seven patients to whom serum was

given for a variety of medical and surgical conditions. Sixteen of these patients received serum transfusion in the treatment of hemorrhage and shock. Various amounts of serum 450-1400 c.c.'s were given and in all instances a beneficial effect was observed. Three cases are reported, all of which were emergency transfusion when a few minutes delay might have been fatal.

In seven cases of shock not associated with hemorrhage, serum transfusion produced a rise in blood pressure, a slower and fuller pulse and improvement in the general condition. These patients were not so critical as those with hemorrhage but restorative measures were necessary.

In seven cases of hypoproteinemia, serum transfusions, were variable in effects. A serum transfusion alone with blood proved a valuable adjunct in the cases of severe burns.

Fourteen patients were treated with serum for a variety of conditions including chachexia, hemorrhage, dermatitis,pneumonia, jaundice, septicemia, and chronic blood loss. None of these cases were carefully studied and the serum transfusion was employed as a supportive measure. In this group, one case of septic mastoiditis could be given no blood transfusion owing to universal

incompatibility. Serum was employed as an alternative measure with beneficial results.

It is believed that serum is an adequate blood substitute for shock. Serum transfusions appear to be just as effective as blood transfusions except in cases in which extensive loss of red blood cells occurs. Serum can be prepared in large amounts without preliminary typing and compatibility tests. Of the forty-seven cases reported in this paper, serum produced only one reaction; pain, followed by redness and swelling in the vein, a condition which subsequently subsided.

There are no great differences betwenn plasma and serum as transfusion fluids. Freshly prepared plasma is serum plus fibrinogen, thrombin and one fifth dilution with 2.5% sodium citrate solution. A fibrin veil and granular precipitate appear in plasma on storage, requiring filtration or centrifugation before administration. However, this may be removed and the plasma stored indefinitely.

The supply of serum is limited only by the supply of blood, and once it is prepared it can be preserved for a long time. Serum can be given without preliminary typing and compatibility tests. No reactions were observed or need be anticipated if serum is properly prepared.

Serum is preferred to plasma because it does not contain sodium citrate and because fibrin precipitates do not occur. (37)

During the last three years the use of plasma and serum as blood substitutes has been investigated. It is clear that there is an adequate replacement of the lost fluid in shock by plasma, when the alterations in physiology are considered.

Plasma is safer and better to use than serum, because its yield from whole blood is greater and it is entirely free from reactions. (35)

Storage at refrigerator temperature is unquestionably best for plasma, as it is for whole blood. However, fifty-three administrations of plasma kept at room temperature for one to 270 days has produced no reactions. It is significant that five of these specimens of plasma traveled 17,000 miles during a period of two months and were subjected to all kinds of climatic conditions. Following this, the specimens were stored in the laboratory for an additional four months. When administered, the plasma had a moderate amount of precipitation and some color change, but proved therapeutically effective.

In the past few years the authors have given 482 infusions with dilute plasma employing a stainless stell

filter in the recipient set, and have had but three reactions, each of which definitely was identified as being pyrogenic in origin.

A clear dilute plasma can be prepared by observing a few simple precautions:

1. The use of fasting donors.
2. The storage of whole blood for more than twenty-four hours before being converted into plasma.
3. The avoidance of shaking whole blood before it is transferred to centrifuge bottles.
4. Refrigeration for approximately twelve hours to permit sedimentation of red cells not removed by the centrifuge.
5. The use of a diluent containing dextrose.
6. The addition of Merthoilate to a concentration of 1:10,000.

Dilute plasma prepared by this method is an effective substitute for whole blood, and even after storage for periods up to nine months under varying conditions, has proved to be a valuable and safe therapeutic agent. (18)

The advantages of plasma are many: It is a more stable system than blood; because of its buffer capacity, it is superior to acacia, glucose, and salt infusions; its isotonic content is of physiologic proportions; it contains certain organic substances necessary for maintaining protoplasmic irritability; and in addition it possesses proteins which are concerned with innumerable

functions of the body economy.

Both plasma and serum restore the irritability of protoplasma. The progressive deterioration of preserved whole blood has become apparent. On the other hand the stability of preserved plasma is now recognized. There are certain advantages of plasma over whole blood, especially over blood stored too long. Amberson, cited by the author, has pointed out these advantages of plasma: Plasma is nonantigenic. Repeated transfusions of plasma have been given without anaphylactic reactions, while repeated blood transfusions are at times dangerous, due to the antigenicity of the acid proteins of the erythrocyte membranes, and the hemoglobin. Plasma is less toxic than serum. (50)

XV

REACTIONS FROM PLASMA TRANSFUSION

Reactions are rare and can usually be traced to the distilled water used, to improper tubing and glassware, or to bacterial contamination. Diggs reports in a series of 266 plasma transfusion, there were no serious serious reactions and only three febrile reactions. A reaction percentage of less than 1%. (13)

Reactions from the administration of plasma are due to the following causes:

1. Toxic citrate in the blood collecting bottle.

2. Pyrogens in the distilled water used in making up the citrate solution.

3. Bacterial contamination of the blood or plasma. Merthiolate inhibits the growth of bacteria for 24 to 90 hours and then is bacteriocidal for many but not all bacteria. Even though these bacteria are dead they may produce severe reactions.

4. The presence of red cell stroma in the plasma often produces an unfavorable reaction in the recipient.

5. If dilute liquid plasma is prepared, care should be taken to make sure the diluent is sterile and free of pyrogens, as this is a source of unfavorable reactions.

6. Improper cleaning or delay in autoclaving the donor sets, aspirating sets and intravenous sets may produce severe pyrogen reactions in the recipient. The above sets should be thoroughly cleaned and autoclaved within four hours after use in order to prevent such reactions.

7. The use of new and poorly prepared rubber tubing in the donor, aspirating and intravenous sets is also a source of reactions.

8. The use of non-fasting donors will occasionally produce an urticarial reaction in the recipient.

9. Reactions may occur from the use of desiccated plasma if the processing has been improperly carried out.

XVI

CONTRA INDICATIONS

In cardiac failure, the heart is unable to pump the blood already in circulation. The giving of plasma not only adds volume, but draws in fluid from edematous tissues thus increasing the circulatory load. Hence in heart failure and in pulmonary edema due to heart failure, plasma is contraindicated. Concentrated plasma proteins may also be contraindicated in patients with hypertension and cerebral symptons. (13)

XVII

SUMMARY

The original investigations with plasma were done on the basis that plasma could be used as a substitute for whole blood. However, recent work has shown that plasma is a therapeutic agent in its own right. There are definite indications for the transfusion of whole blood, but they are few as compared to the indications for the transfusion of blood plasma.

In the past, blood transfusion has been indicated in specific diseases such as shock, hemorrhage, burns, septicemia, etc., in which it was assumed that the

benefit derived from the transfusion was from the red cells. In the light of present knowledge, the indication for a transfusion exists only when clinical or laboratory evidence show a changed physiology.

Following a reduction of blood volume, severe enough to cover diminished blood pressure, and the appearance of clinical signs of shock, the restoration of blood volume is imperative. This can best be accomplished by the transfusion of blood plasma even when the loss of blood has been great.

In various kinds of shock, from burns or circulatory failure when there has been no loss of blood, the red cell count will be found increased. The increase is due to a loss of blood volume and not an actual increase of red cells. Damaged capillaries which have become permeable to proteins permit the passage of plasma proteins from the blood to the tissues. This is particularly true in the traumatized, burned or diseased areas. In these areas the concentration of plasma protein is sufficient to remove large quantities of electrolytes and water from the blood, thus further reducing blood volume.

All investigators of shock, although they may differ as to the mechanism of shock, are agreed that blood volume must be restored. As our knowledge of the disturb-

ed physiology of shock has increased, it has become evident that the plasma in blood transfusion rather than the red cells is responsible for the clinical improvement.

Depleted blood plasma protein is another indication for blood plasma transfusion. Clinical edema occurs when the plasma proteins are reduced below 4.5% from a normal of 6.5% to 7.5%. When plasma proteins can be restored and maintained by the oral ingestion of proteins, that is unquestionably the optimum method. However, when this is not possible, the only was protein can be furnished will be by the parenteral route.

Plasma has many advantages over whole blood:

1. Blood plasma can be preserved at refrigerator or room temperature for very long periods.
2. It can be transported safely over long distances without special precautions and can be carried in the physicians bag for use in the home when needed.
3. Plasma can be administered with the simplicity of other parenteral fluids; intramuscular as well as intravenous administration is possible.
4. Typing and cross-matching is unnecessary.
5. The danger of incompatible reaction is eliminated.
6. Plasma can be administered much more quickly because it is always ready for immediate administration.

The above mentioned advantages of plasma would be unimportant if plasma were not equally as satisfactory,

or more satisfactory than whole blood. When the indication for transfusion is considered from the point of view of the physiological changes that occur in disease, it will usually be apparent that restoration of blood volume and plasma protein is more important than restoration of red cells. (19)

The therapeutic effectiveness of plasma in burns and in the hypoproteinemic state cannot be questioned. Blood serum was used for most of the experimental work in animals. The authors have used human blood plasma exclusively for many reasons; namely, the greater yield, simplicity of separation, freedom from reactions, and because out-dated blood in their blood bank is an important source of plasma.

The elimination of typin and cross-matching, simplicity of administration, safety of long storage, transport ability and equal effectiveness makes plasma a satisfactory substitute for whole blood. Although donor plasma agglutinates in the cells of the recipient when cross-matched, there is apparently no destruction of recipient cells when such plasma is transfused. This has been proven by 521 administrations under their supervision and thousands of administrations by others. Plasma stored at room temperature for periods up to 26 months has been administered without reaction, and with

satisfactory clinical results.

Plasma is equally as effective as whole blood in the treatment of shock, hemorrhage, burns, and hypoproteinemia. Its effectiveness in traumatic shock clinically manifested by a diminished blood volume with the loss of plasma from the circulating blood is generally recognized.

The picture of shock from hemorrhage is identical with that of shock from trauma. Shock may follow a minor hemorrhage or may not occur after severe hemorrhage. The clinical signs of shock from hemorrhage are clinical signs of shock from hemorrhage are clinical manifestations of reduced blood volume with resulting tissue anoxia. Whole blood transfusion is the best treatment for severe hemorrhage if administered early. In the zone of the Interior, where base hospitals have whole blood available, the time required to prepare for a transfusion is short. However, in the Communication Zone and in certain portions of the Combat Zone, there are many casualties that are in need of immediate transfusion. Under these circumstances, whole blood transfusion is either impossible, or the delay will more than counteract any benefit which might be derived from the administering of red cells. In severe hemorrhage,

the preservation of life depends upon the early restoration of blood volume. This restoration can be accomplished with blood plasma alone.

The use of plasma as a substitute for whole blood has passed through the experimental stage, and is now a recognized therapeutic agent. Its effectiveness in shock, hemorrhage, burns and hypoproteinemic state is now longer questioned. Its usefulness during was is being proved in the present conflict. The simplicity of the technique presented, its ready adaptability to existing facilities, and its proven efficiency make it possible for many institutions to enter into any program for the preparation of plasma in large quantities.

XVIII

CONCLUSION

Circulatory failure starts when blood volume begins to decrease. In circulatory failure, regardless of the cause or precipitating factor, the clinical manifestations are a result of reduced blood volume. In circulatory failure, the reduction of blood volume is due to loss of blood plasma through permeable capillary walls. Loss of plasma is accompanied by concentration

of the erythrocytes, which due to decreased blood volume and lowered pressure, are unable to circulate and function properly. This concentration of erythrocytes does not increase the oxygenation of tissues, but does increase the viscosity of the blood. This increased viscosity further impedes circulation. Failing circulation inevitably results in anoxia. With this in mind we must assume that in shock without erythrocyte loss„ restoration of blood volume by plasma should be more desirable than restoration by whole blood, Clinically the use of blood plasma has given highly satisfactory results.

Plasma has proven therapeutically active after two years of storage at room temperature, but stored at ice box temperature is recommended.

It is preferable to administer plasma directly into the blood stream, however, it can be given outside the blood stream with the same therapeutic results. Clinical observations indicate that circulatory failure is much easier to prevent, then to treat after it is firmly established. The judicious use of plasma and parenteral fluids early in the course of severe illness will lesson the danger of circulatory failure to the patients and spare the clinician much anxiety.

Some definite conclusions can, therefore, be made.

1. Circulatory failure can be anticipated in every severe illness.

2. Treatment should be instituted before clinical manifestations appear.

3. The clinical manifestations of circulatory failure are primarily due to a reduced blood volume.

4. Loss of plasma is responsible for the reduction of blood volume, and it should be replaced with blood plasma.

5. Blood plasma is equally as effectively as whole blood in the treatment of circulatory failure.

6. In children where intravenous medication is difficult, plasma may be effectively administered intramuscularly or subcutaneously.

7. Typing and cross matching are unnecessary when blood plasma is used by any route of administration.

8. The use of stored plasma simplifies the adequate treatment of circulatory failure.

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