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Use and indications for blood, plasma, and serum transfusion

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The Use and Indications for Blood,

Plasma, and Serum Transfusion

by

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FOREWORD

The purpose of this paper is to investigate the use of and indications for blood, and plasma or serum transfusions. Much of this work is in the experimental stage; and as is expected in this type report, the contents are of a plagiaristic nature.

My plan is to divide the paper into three parts. The first part deals with the history of blood transfusion and the beginning history of plasma and serum transfusion. As regards the latter, history is now being made.

The second division deals with the clinical and experimental evidence related to the use and indications for plasma, serum and blood transfusion. Where sufficient work had been done on one phase of plasma and serum, these phases have been written up under the headings of shock, burns, nephrosis, intestinal obstruction, and increased intracranial pressure. The more or less isolated work has been delegated to the usual miscellaneous division.

The third division is my own attempt to rationalize these procedures on the basis of the evidence presented in the second division.

PART I

HISTORY

Even in ancient Egypt, the vital importance of blood to the human system was appreciated. The writings of the ancients, however, refer to the mystical attributes of blood in all their considerations. Thus, it was thought to carry in it virtues such as youth and health of its possessors. Even in the Old Testament it was considered a fit sacrifice to the gods for this very reason. From earliest historical times the use of blood as a therapeutic agent has been advocated, some people believing that blood not only carried the vital forces of the body but also was the seat of the soul(1). Sensing the recuperative and resuscitative value of blood; the Egyptians, of course erroneously, tried to gain its benefits by bathing in it(2).

Thus Pliny and Celsus described the custom of the Romans who rushed into the arena to drink the blood of dying gladiators. The Egyptians, Hebrews, and Syrians were supposed to have used transfusion, but here confusion arises as is seen in the obscure references and vague and contradictory literature due to the fact that in the Middle Ages, the drinking of human blood (ingestion) and transfusion were confused(3). Such confusion arises in the record of the often cited "Transfusion" of the blood of three youths into Pope Innocent VIII in 1492 which, by the way, was a complete failure. Because of historic interest and because of the confusion just mentioned, I will requote the record so that the reader may interpret as he will.

"The vital powers of Innocent VIII, rapidly gave way; he had for some time fallen into a kind of somnolency, which was sometimes so profound that the whole court believed him to be dead. All

means to awaken the exhausted vitality had been resorted to in vain, when a Jew doctor proposed to do so by the transfusion, by a new instrument, of the blood of a young person, an experiment that had hitherto only been made on animals. Accordingly, the blood of the decrepit old pontiff was passed into the veins of a youth, whose blood was transferred into those of the old man. The experiment was tried three times, and at the cost of the lives of the three boys, probably from air getting into their veins, but without any effect to save the Pope(4). Probably the most truthful account is that of Mathews who states that the blood was administered as a draught since it is highly improbable that blood transfusion could have been practiced at a time when the circulation of the blood was not yet recognized.

Hieronymous Cardanus (1505-1576) and Magnus Pegelius proposed the transfer of blood directly from the blood vessels of one individual to those of another. Andreas Libavius (1615) definitely advocated blood transfusion describing a technic similar to that used until recently. He wrote: "Let there be a young man, robust, full of spirituous blood, and also an old man, thin emaciated, his strength exhausted hardly able to retain his soul. Let the performer of the operation have two silver tubes fitting into each other. Let him open the artery of the young man, and put it into one of the tubes, fastening it in. Let him immediately after open the artery of the old man, and put the female tube into it, and then the two tubes being joined together, the hot and spirituous blood of the young man will pour into the old one as it were from a fountain of life, and all of his weakness will be dispelled." (after Scheel after

Wiener). It is doubtful that Libavius carried his proposal out, and it is thought by some that he considered the procedure ridiculous and contemptible and was being ironic in his extravagant claims.

The actual history of blood transfusion as we understand it today should begin with the discovery of the circulation of blood by Harvey in 1616 and the publication in 1618 of his immortal monograph, "exercitatio Anatomica de Motu Cardis et Sanguinis in Animalibus." All procedures previous to this must necessarily be regarded with doubt.

It was not until after the middle of the seventeenth century that authentic accounts of transfusions are to be found. In the writings of Francisco Folli, as Florentine physician, it is claimed that a demonstration operation of transfusion of blood was made on Aug. 16, 1554, before the Grand Duke Frederick II; but confirmation does not seem to be available in the writings of others(5).

Christopher Wren, one of the most active members of the Royal Society in England was responsible for many new experiments in several sciences. It was Wren that experimented with dogs by injecting substances such as ale, wine, scammony, and opium into the veins by means of slender quills fastened to bladders. Thus stimulated, Wren's friend, Richard Lower, known for his work on the anatomy of the heart, used a quill cannula for obtaining continuity between the artery of one animal and the vein of another animal. Lower is therefore credited with having performed the first authentic blood transfusion in England while working in the laboratory of Thomas

Willes at Oxford in 1665. His written account which is quite difficult to follow can be read in Philosophical Transactions, Monday Dec. 17, 1666, pp. 353 et seq. I quote a short passage, "All things being thus prepared, the dogs on their sides toward one another so conveniently, that the Quill may go into each other (for the Dog's necks cannot be brought so near, but that you must put two or three several, Quills more into the first two to convey the blood from one to another". After that unstop the quill that goes down into the first dog's Jugular vein, and the other Quill coming out of the other dog's Artery; and by the help of two or three other Quills put into each other, according as there shall be occasion, insert them into one another. Then slip the running knots, and immediately the Blood runs through the Quills, as through an Artery, very impetuously. And immediately as the blood runs into the Dog, unstop the other Quill, coming out of **the** upper part of his Jugular vein - - - - - ; and let his own blood run out at the same time into Dishes (yet not constantly, but according as you perceive him able to bear it) till the other dog begins to cry, and faint and fall into convulsions, and at last dies by his side."

At a meeting of one of the learned societies held at Paris in July 1658, Des Gabets announced that a friar, Elroy Pichot, had made for him in 1651 an instrument consisting of two small silver cannulae, connected by a leather purse about the size of a walnut and fitted with valves so that blood in its transit could not return into the emittent but would be forced onwards into the afferent vein.

There is some dispute but little doubt that the first transfusion into a human was done by Denis and Emmerez of France. In March 1667

they began transfusing from dog to dog and later from calf to dog.
On June 16, 1667, Denis and Emmerez transfused blood from a lamb
into a youth 15 or 16 years of age, "who had been tormented for
more than two months with an intractable and violent fever." An
interesting account of his transfusions in animals and the first
two in man may be found in Philosophical Translations July 22, 1667.
The first transfusion was successful, and encouraged by his success,
Denis performed other similar operations.

In October of 1667, Gaspar de Gurye made some remarks concern-
ing the first warning of the dangers attending the administration
of incompatible blood. De Gurye remarked "that an expert Aquaintance
of his, transfusing a great quantity of blood into several Doggs,
observe alwayes, that the receiving dogs pissed Blood." In a long
account of his second transfusions in man, Denis describes for the
first time the phenomena of hemolysis and its attendant symptoms.
In this case the blood of a calf was used in a massive transfusion.
He remarked that the patient "made a great glass full of Urine, of
a colour as black, as if it had been mixed with the soot of Chimneys."
A full account of this may be read in Philosophical Translations of
Oct. and Nov. 1667.

During this time the English also had been experimenting with
transfusion. Samuel Pepys records on Nov. 21, 1667 the case of Dr.
Wilkins, who was a "frantic" minister transfused with 12 oz. of
sheeps blood after having been given 20s for his consent.

The success of transfusion in France and England soon led to
more frequent use of the discovery; and as we might expect, fre-

quent and fatal reactions were met with. Some of the people still feared that the transfusion of animal blood into humans might give rise to growth of horns etc. in the latter. It is said (Jennings) the Faculty of Medicine at Paris still refused to accept the Harveian circulation of blood and set to work to publish anonymously pamphlets against Denis and Emmerez. It is said that these physicians bribed the widow of an unfortunate lunatic to charge these operators with the death of her husband. She gave Denis so much grief that he lodged a complaint against the widow and those who supported her in court. The court prohibited the performance of the operation in the future except with the sanction of the Faculty of Medicine; and the necessary permission was, of course, withheld.

For the next 150 years, little was done for the use or advancement of transfusion. It may be said that James Blundell, lecturer of physiology and midwifery at St. Thomas's and Guy's hospitals, rediscovered transfusions. He was stimulated by the terrefic morbidity in post partum hemorrahage cases. His were the 1st scientific experiments along these lines and his paper published in 1818 showed the thoroughness with which he investigated the problem. His experiments were first performed on dogs and at first consisted of withdrawing blood from the femoral artery and reinjecting into the femoral vein to determine whether or not blood would loose its properties after having been passed thru an instrument. He then conducted a long series of experiments on dogs as regards the properties of blood, the effects of its withdrawal, and the resuscitation of an exsanguinated animal. These experiments not only corroborated those already made by others as to the success of direct

and indirect transfusion between animals of the same species, but also conclusively proved that so far as lower animals are con-er-ned at least, it is an unsound and dangerous practice to transfuse alien blood. In 1824 he published some results of transfusion in humans. His appartus, which he called the Impellor, consisted of a funnel-shaped receptacle for the blood; and a syringe incorporated into one side of the funnel contained a complicated system of spring valves which caused the blood to travel along the delivery tube when the plunger was pushed down. Blundell's statistics would seem to give unfavorable evidence as to the worthiness of transfusion, but it must be recalled that he used it only on patients who were exceedingly ill or nearly dead. He was convinced however, that transfusion by the syringe was quite feasible and would find its place in general practice. He first tried transfusion on four patients who were moribund, but later was successful in three women patients in whom death from post partum hemorrhage seemed certain. It may be said that the chief contribution of Blundell was a revival of interest in the use of transfusion.

One of the chief obstacles at that time was the difficulty of transfusion without coagulation of the blood. Bischoff, in 1835, sought to overcome the difficulty by injecting defibrinated blood. The advances of the next few years were concerned for the most part with improvement of apparatus and attempts at prevention of coagulation. In 1857, Higginson applied the principle of a rubber syringe with ball valves for transferring the blood of the receptacle into which it was drawn, into the vein of the recipient. He report-the successful application of the syringe in seven cases. As a

further attempt at anticoagulation, the use of small quantities of ammonia was suggested by Richardson, in the Guy's Hospital Reports in 1858. In 1859, Martin reported a series of 57 cases (obstetrical) in which 43 were successful. Blassius, in 1863, reported a series of 116 transfusions during the previous 40 years in which 56 were satisfactory. These do not indicate a remarkable degree of success, but it must be remembered that fatalities frequently occurred attended by symptoms we have learned to associate with incompatability. At that time, these reactions were thought to be due to the introduction of air bubbles during the procedure. In 1869, Braxton-Hicks suggested the use of phosphate of soda as an anticoagulant and used it in four obstetrical cases, but the phosphate was found to be harmful.

In the years around 1875, transfusion was still regarded as procedure to be used only as a last resort. Even at this time, the blood of other animals was being used for transfusion although the practice had been discredited by Panum in 1865 and others. It was sentiment as much as science that fortunately limited this procedure. From this time on, many of the historic events occurred in our own country. Also at this time, the combination of serious reactions from use of animal blood and the introduction of physiological saline in treatment of hemorrhage tended to throw transfusion once more into disrepute. Hirudin was tried as an anticoagulant in 1892 at the suggestion of Landois, but was discarded because of its toxicity. In this same year, Von Ziemessen successfully performed a blood transfusion by drawing 20 cc. of blood at a time into a syringe from the donor's vein and injecting it into that of the recipient.

In 1895, Quierols suggested the intima cuffing rings; and in 1897, Murphy's work on blood vessel surgery helped to find a solution to the great problem of coagulation of blood by permitting direct transfusion without the intervention of any tube.

Perhaps the most significant milestone in the history of the development of transfusion was the discovery of iso-agglutination. Considering the terrific number of cases which were transfused before the discovery, we wonder not that there were many fatalities but that all cases were not fatalities. The literature is extremely diverse as regards the discovery of iso-agglutination. Both Shattock and Landsteiner have been credited. In the original article by Shattock(6), it is found that Shattock was concerned primarily with the phenomenon of chromocyte (r.b.c.) clumping in acute pneumonia and other diseases. Early in his work, he noted that horse serum caused agglutination of human red blood cells and later found agglutination to occur when serum of acute pneumonia patients was mixed with normal human blood. While reading this original account, one anxiously waits for a description of results of mixing serum of one normal human with blood of another normal human by way of control, but Shattock does not describe such a control. Therefore, it must be admitted that agglutination was seen and described first by Shattock as an incidental finding but that Landsteiner was the first to control and rationalize the phenomenon as one occurring in normal human blood mixtures. Landsteiner, in 1900, showed that the serum of one normal human being can agglutinate or hemolyze the bloods of certain other individuals. This was undoubtedly the most important real discovery relating to blood transfusion, and Landsteiner

himself(7), fully realizing the practical significance of his findings, pointed out the importance of the blood groups for blood transfusion in his original paper on blood groups. Landsteiner divided blood into three groups. Descatello, and Sturli found the fourth group in 1902 and there were the possibilities of selection of donors and elimination of severe reactions which sometimes followed in sudden death. Also in 1902, Carrel began his artery-vein anastomoses for direct transfusion. His technic was extremely delicate and he reported in 1906 a case of direct anastomoses between a father (eminent N.Y. surgeon) and his son who had hemorrhagic disease of the newborn. At this time (1906), Ottenburg at Mt. Sinai Hospital had a set of silver cuffing rings made and used them on transfusion on dogs.

1907 was a good year for transfusion advancement. Crile put the technic of direct transfusion on a more secure basis than it had ever been before. He devised a method of connecting the artery of the donor with the vein of the recipient by drawing the vein of the recipient through a small cannula and cuffing it back over the cannula. The artery of the donor was then drawn over the vein to give a continuous lining of intima to favor anticoagulation(8). In the same year, Hektoen made the plea that blood groups be made the basis for selection of donors for blood transfusion(9). Jansky independently, determined the four blood groups into which humans can be classified in 1907.

Ottenburg and Shultz were probably the first to use Landsteiner's discovery for determination of compatibility in an actual transfusion(10). It was the independent work of Moss on blood grouping

1910 that seemed to draw the attention of the profession and give

blood grouping the importance it discovered but had not until this

got.

Simplification of the group tests soon followed; and at the

same time, improvements were made in the use of syringes, paraffined

tubes, and anastomoses of the blood vessels. Curtis and David, in

1911, introduced the syringe transfusion through a two armed tube

coated on the inside with paraffin. Kimpton and Brown, in 1913,

performed indirect transfusion by means of the paraffined vessel and

the objection of the permanent destruction to arteries was over-

come. At the same period, Lindeman developed the multiple syringe

technic by using a large number of syringes and employing an assis-

tant who kept them clean with sterile saline. At this time, Otten-

berg and Kaliski reported 128 of their cases of blood transfusions

in which three cases of reactions between the patients' serum and

the donors' cells were found by agglutination tests. Of these three,

one developed anuria and died 8 hours after the transfusion. Blood

smears on these patients showed phagocytosis of red blood cells;

and smears taken when bloods of recipient and donor were compatible,

showed no such reaction. Hemolytic reactions reported by other men

at this time were also shown to be due to incompatibility.

In 1914, Moss reintroduced the defibrination technic. In this

same year, Hooker and Sattirlee tried hirudin as an anticoagulant

(suggested by Landois in 1892) but found it was apparently quite

toxic. At the same time, Hustin of Belgium used sodium citrate and

glucose as an anticoagulant; and on November 14, 1914, Professor

L. Agote of Buenos Aires performed the first transfusion of citrated

blood. History was made on that date, because although it had long been known that hirudin or leech extract, oxalic acid, or citric acid could be used as anticoagulants outside the body, their supposed toxicity had prevented their being used in transfusions. Now it was demonstrated that sodium citrate could be used; and in 1915, Lewisohn and Weil independently perfected the citrate technic and standardized the dosage so as to make it non-toxic but still efficient as an anticoagulant.

Mostly due to Lewisohn's work, it has been said (Keynes), a method has been discovered which approached the ideal since it united the four cardinal criteria of simplicity, certainty, safety, and efficiency. It might be well to mention the technic developed by Unger at this time. By making use of a syringe with a four-way stopcock, he devised a means of transfusing large measured amounts without undue hardship on either the donor or the recipient.

It seems as if the great advances at this time were in anticipation of the terrific need for transfusion which was to be manifest in the World War I. The British admit they knew very little of transfusion in the first two years, and it seems the French and German doctors were similarly inadequately informed. We should be proud of knowing it was the reinforcement of the British Army Medical Corps by medical officers from the United States in 1917 that spread knowledge of blood transfusion throughout the armies.

Since that time, the major advances have been concerned with the immunological aspects of blood groups, clarification of the mechanism of certain transfusion accidents, the use of stored blood (preserved blood and blood banks), the introduction and use

of dilute and concentrated plasma and serum for transfusion. The World War I gave great impetus to the transfusion of whole blood containing citrate as an anticoagulant and introduced the use of stored blood on a moderate scale.

The earliest history of the use of plasma and serum is more difficult to find and is, as a matter of fact, still being made. With the amount of work being done and the excellent results obtained, an exhaustive search will necessarily be made by someone to confirm claims of priority. In my reading, which was by no means exhaustive, I was unable to find the earliest work done on plasma and serum. It seemed to have just gradually started everywhere at once. There were several articles, however, which show it was used, at least experimentally, during World War I. In 1918(11), several men worked with rabbits in an attempt to determine the amount of Hb (red cells) that could be extracted abruptly and still permit survival of the animal. They bled rabbits and then tried injecting 2% and 3% acacia, normal salt solution, and plasma. The plasma was more or less ignored in their interest for acacia, but they recognized that the other solutions were of temporary benefit only. In 1919(12), a group manipulated the intestines of dogs to produce shock with its drop in blood pressure. In treatment of the shock, they used general measures (heat, position, etc.), special methods (rebreathing, strapping limbs, etc.), drugs (none of value), and restoration of fluid volume. In this last category, they tried many solutions and recognized that sale solutions leaked out of the vascular system and that blood gave the best results excepting serum. Here again the serum therapy was ignored or considered as of minor

significance.

The use of stored blood was just attempted in the World War I and has been increased materially since. Weiner reported in 1939 (13) that 14,000 such transfusions had been given in the U.S.. Limitations of the use of stored blood vary in proportion to its state of preservation and the number of changes that occur in the blood itself.

Another more recent development is the use of cadaver blood for transfusion. In 1928, Shamov transfused blood from dead to living dogs with success. The real interest mounted when Judin, a Russian worker transfused cadaver blood in humans in 1930. A would-be suicide who had slashed his wrists and lost a large amount of blood was brought to Shlifasovski Emergency Hospital. Six hours before, an old man had died of a heart attack in this same hospital. Hurriedly, the veins of the dead man were incised; and the blood was collected and injected into the collapsed veins of the dying man who was scarcely breathing. In a short time, the dying man recovered consciousness. Other cases followed. Judin found that in sudden, painless, deaths, the blood remain liquid and will flow out by gravity after 24 hours. He now has all such death cases sent in and extracts the blood which he uses or keeps with citrate in refrigerators for as long as 20 days.

In the past few years, there has been marked progress in blood transfusion. This has been largely due to popularization of the rapid nitrate method, and the reduction of frequency of reactions had stimulated the use of transfusions throughout the world. One

of the greatest recent contributions is probably the use of stored

blood and especially stored cadaver blood as found by the Russian

workers mentioned above and used extensively in the Spanish Civil

War. Although the hemolytic transfusion reaction has been clari-

fied by a host of workers, its pathogenesis, treatment, and occurr-

ence in transfusions which appear in vitro to be compatible, are

problems yet to be solved(15). Aspects now being investigated are

immunotransfusion in certain infections, the value of serum in shock,

burns, edema and protein deficiency, and the properties and limita-

tions of preserved blood.

The serum and plasma aspect, as well as the preserved blood tech-

nic will probably be developed in World War II as was whole blood

transfusion in World War I.

At any rate, that history in these last respects is only now

being made is a fact which will be recognized in the following pages

to which much was contributed by the direct or indirect information

from the British Medical Corp.

PART II

CLINICAL AND EXPERIMENTAL EVIDENCE

SHOCK(INCLUDING THAT ASSOCIATED WITH HEMORRHAGE).

Before reviewing a portion of the recent literature on the use of plasma and serum in the treatment of shock; it is proper, I think, to attempt a definition of shock and to cite an experiment which is not so recent but which will review the findings in shock. With these findings in mind, it is easier to follow and rationalize the work of the various men in this phase of work.

Shock can be divided into primary and secondary types. Primary shock is the state of collapse which follows immediately after some injury. It is attended by a fall in blood pressure, slowing of the pulse rate, pallor, and unconsciousness. The common faint is a simple form of primary shock and recovery usually occurs when the subject falls and thereby restores cerebral circulation. Secondary shock is more difficult to define and is the one that this paper is to deal with. It is the acute circulatory failure that follows a variety of causes such as following extensive surgical operatins, burns, war wounds, and severe accidents. The clinical aspects are low blood pressure, pale or gray skin, moist or sweaty skin, cold, clammy extremities, restlessness, decreased sensitivity to pain, subnormal temperature, and the appearance in one to several hours after the associated cause. The most outstanding feature is the fall in blood pressure. Fortunately, it is not the purpose of this paper to state or discuss the cause of shock(i.e. the essential or physiological cause).

The experiment mentioned above and which will show the pathologic findings in shock is one of the many done by Blalock and

Beard in 1932(16). They used dogs under intraperitoneal anaesthesia in their experiment. To produce shock, they opened the peritoneal cavity and then passed the intestines continuously through their fingers. With the experiment well controlled, they collected and analyzed the fluid escaping into the peritoneal cavity. Studies were first made of the blood serum and the peritoneal fluid during the trauma and with no fluids being administered. They found that there was a great diminution of the volume of blood plasma in circulation, but that the total protein content per unit volume of blood serum remained constant. They also determined that the total protein content of the blood serum and the peritoneal fluid were approximately the same in all instances but that the albumin content of the peritoneal fluid was greater than that of the blood serum and that the reverse was true of the globulin fraction. From this, several deductions can be made. First, there was a decrease in intravascular total plasm protein but not in the apparent plamma protein. As shall be seen in several following papers by other men, there has been found a decrease in both the total and apparent plasma protein. Second, the plasma-like peritoneal fluid contained more albumin than globulin showing that the smaller albumin particles escaped from the vascular system more quickly and readily than the globulin fraction. These men next injected various solutions intravenously while the trauma was going on. They found that the intravenous injection of saline and glucose was associated with a decrease in the percentage of protein per unit volume of serum, a diminution of the volume of plasma in the circulation, and a great decrease in the absolute plasma protein. When gum acacia was used, there was a decrease in the percentage of protein, an

increase in plasma volume, and decrease in the absolute amount of plasma protein. When serum was used intravenously, there was a very small change in the percentage of protein, volume of plasma, and absolute amount of plasma protein. Intravenous whole blood was associated with a very small change in percentage of protein in blood serum, a tremendous increase in blood concentration associated with a decreased plasma volume and a decrease in the absolute plasma protein.

E. B. Mahoney(17) produced experimental shock by cooling the peritoneal cavity of dogs and also by traumatizing an extremity. The general condition and the blood pressure readings were his criteria of the state of the animals. He then compared the effects of plasma with those of whole blood, saline, and acacia as regards therapeutic value. In shock produced by cooling the peritoneal cavity, there was an excessive loss of plasma protein from the circulating blood, and albumin constituted the major portion of this loss. In this case, plasma was found to be the most efficient therapeutic agent in restoring the normal blood pressure. With plasma, the increase in blood pressure was more rapid and striking than with blood. His results showed that plasma was more efficient in treating experimental shock associated with excessive plasma loss than in treating that due to trauma to an extremity. In the latter, plasma caused only a temporary return of blood pressure. He believes that shock produced by these two methods differs; and that in the first instance, the shock is much like that of humans caused by burns, operations in the peritoneal cavity where little bleeding has occurred. He also feels that the traumatic shock was more like the shock

caused in humans by acute hemorrhage. On the basis of his experiments, the work of others and clinical evidence, Mahoney has adopted certain views. He feels that injury causes traumatic shock by circulatory collapse and a decrease in circulating blood volume which is not entirely understood but is due in part to both obvious and concealed bleeding at the site of injury plus excessive loss of blood plasma in the traumatized tissue. In acute hemorrhage, if bleeding is stopped before too great amount of blood is lost, the body tends to build up the depleted volume by drawing fluid from the tissue spaces to cause an increase in blood volume; and the intravenous injection of saline can restore volume to normal limits. In traumatic shock on the other hand, there is greater loss of plasma due to increased permeability of small peripheral vessels so that saline dilutes the remaining plasma which causes a decreased osmotic pressure which in turn aids in further loss of plasma. Thus traumatic shock differs from that due to acute hemorrhage(loss of whole blood), and that associated with burns and intestinal manipulation(blood plasma depletion).

Bond and Wright(18), in an experiment which is much refered to in the literature used lyophile serum in the therapy of shock produced in dogs. Lyophile serum is that obtained by rapid freezing and rapid dehydration under a high vacuum while frozen. The serum thus obtained is not only rapidly soluble in water but is believed by many to retain all the solid elements of normal serum. They used dogs in which shock was induced by trauma to the gut, or to an extremity, or by acute hemorrhage. The blood pressure readings were the criterion of effect in this well controlled experiment.

In all cases, the results were good when serum was used(better than acacia), and the blood pressure was raised and maintained _for_ _at_ _least_ _several_ _hours_. Although the control animals all died, these men themselves mention that should have been observed over a longer period of time and that the results are not to be transferred too readily to humans. They believe that in secondary shock, the decrease in circulating blood volume is most commonly regarded of being centrally important occurence; and that although the mechanism is not understood, many stress the fact that plasma was the portion most severely reduced and that the escape of plasma proteins is very important. In clinical treatment they believe that the immediate availability of lyophile serum, its therapeutic suitability, and its action upon shocked animals suggest its use as a valuable treatment for shock and hemorrhage. I might say that the fact that these men watched the animals for only several hours has been a subject of criticism in other articles, but the very fact that they got results for this length of time has been seized upon by the British who, as will be seen later, need such an effect in acute hemorrhage cases until blood is available.

In a communication to point out that plasma is available safely, immediately, and cheaply to anyone having access to a blood bank, Lehman(19) points out some of the indications for plasma transfusion. Although he cites no evidence or experimental source, his ideas are interesting. "The intravenous administration of blood plasma is recognized as a rational procedure in the therapy of secondary shock resulting from loss of blood plasma and consequent increase in concentration of the blood, as in crushing injuries and burns. Although whole blood transfusions are of therapeutic value

in these conditions, the red blood cells serve no useful purpose and tend to prevent the rapid correction of increased blood viscosity. It can be said, with possibly some reservation that plasma transfusion also appears to be logical in hypoproteinemia resulting from a combination of starvation and parenteral administration of crystalloid solutions in the treatment of acute abdominal disease. More recently, Strumia, Wagner, and Monaghan(20) have used citrated plasma in the treatment of patients in secondary shock. They cite ten cases of secondary shock in humans. Of these, four were cases of postoperative shock without excessive blood loss. In these, intravenous injection of citrated plasma was enough to initiate rapid recovery in three and the other case had blood in addition. One case of severe traumatic shock without visible blood loss made a rapid and complete recovery after the intravenous injection of plasma. In one case of traumatic shock with hemorrhage, intravenous plasma rapidly and efficiently contributed to the restoration and maintenance of circulation until whole blood was made available. One case of postoperative shock with small hemorrhage and one case of traumatic shock with small hemorrhage were treated with intravenous plasma which restored circulation until blood was given. There were also two cases of the type in which the traumatic lesion is of the nature and extent that often leads to development of shock. It is the impression of the authors that plasma was of material value in preventing collapse. These men feel that plasma is the ideal material for permanent reestablishment of proper circulation in secondary shock and believe that it should be used to avoid altogether the emergency transfusions(blood) with their unavoidable delays and dangers of hurried preparation. The advantages

of plasma in these cases are ease of preparation and transportation, preservation in storage, freedom of reactions, and the fact that it is immediately available to be used in large and even repeated doses. They believe that blood has its value after the plasma has relieved the shock. In reports of this kind, as is the case with nearly all therapeutic tests, it is difficult to control the cases; and I feel that the results should not be considered invalid because of this.

Although the experimental or clinical evidence is not available, a second-hand report on work done by Buttle of Middlesex Hospital can be obtained in the Current Comments(21). The present World War has stimulated studies on effective substitutes for blood transfusion in treatment of hemorrhage, and Buttle reported an evaluation of blood substitutes based on controlled experiments in animals. In order of therapeutic value they list 1. plasma, 2. serum, 3. hemoglobin-Ringers, 4. gum saline, 5. suspended red cells, 6. isotonic saline and glucose. It is also said that although the British felt that plasma and serum are equally effective, serum offers certain advantages in collection since it can be dried easier.

In an attempt to evaluate serum as a blood substitute in the treatment of hemorrhage and shock, Levinson, Neuwelt, and Necheles (22) experimented with dogs. In one series, dogs were bled to produce shock and were then infused both immediately and after a delayed period($1\frac{1}{2}$ hours) with fluids. Another group was subjected to massive hemorrhage and delayed infusion. A third group had graded hemorrhages. In the first group, it was found that blood serum was

more lasting in effect even if the transfusion was delayed than was
immediate saline solution. In the group with massive hemorrhage,
serum and blood gave the best results and saline caused further
lowering of the serum proteins. In the graded hemorrhage dogs,
those receiving blood or serum lived and those getting saline died.
Throughout the experiment, only a few reactions were noted and these
were transitory in character. From this and other experiments
and from clinical experience, these men have developed a concep-
tion of shock which is worth speaking of. Acute, severe hemorrhage
causes oligemia, a resultant lowered blood pressure, and primary
shock. The outcome of this shock, they feel, depends upon the rate
and am't of hemorrhage and the availability of the blood reserves
(of the body). In such cases, the prime need is the restoration of
fluids and the maintenance of sufficient circulating volume. The
actual composition of the fluid is of secondary importance; and if
the primary shock and oligemia is not relieved promptly, the tis-
sue anoxemia, increased capillary permeability, and acidosis(i.e.
secondary shock) occur. Secondary shock presents a different pro-
blem than does the primary shock; and saline is not, in secondary
shock, the life saving measure that it is in primary shock because
the capillary permeability has increased. Serum, on the other hand,
cause a marked and sustained increase in blood pressure.

In the graded bleeding experiment, saline and glucose merely
leaked through the increasingly permeable capillaries while serum
did not. The serum remained intravascular. In the massive hemorr-
hage group, they found that whole blood is the best restorative,
but serum overcomes all the effects of hemorrhage in dogs except

the loss of red blood cells(which they found could be quite extensive without serious effects).

They feel that although blood is the best restorative agent, much of its good effect is lost in the time consuming laboratory tests preliminary to administration. Serum may be given in massive doses without delay or preliminary typing because pooling of serum partially suppresses the iso-agglutinins and the patients blood further inhibits the iso-agglutinins. They therefore believe that if serum is as effective in overcoming the effect of hemorrhage in man as it is in dogs, it not only can be used as an interval measure preceding blood transfusions, but also as a substitute measure when blood is not available or when red blood cell loss is not too extensive. As an emergency therapeutic aid, serum should prevent the development of shock. For these reasons, Levinson etc. feel that serum as a blood substitute, should find wide use both in civil and in battle front emergencies. They have used serum in a limited number of human cases with results as good as those they found in dogs. (In a personal communication to Magladery, Solandt, and Best, the results of the above animal experiment were recently applied to humans with excellent results.)

Edwards, Kay, and Davis(23) have written an article which shows the trend of British thought as regards this subject. They repeat the conception that wound shock causes a change in the capillaried allowing the exudation of fluid out of circulation and this in turn produces a decrease in blood volume with higher concentration of red blood cells than plasma proteins. They also have the idea that the primary requisite as regards treatment is the restoration of

volume. They say that unless there has been hemorrhage of great proportion, plasma is most efficient as a therapeutic agent. In speaking of post operative shock and post-operative pulmonary edema, they have said that this type of shock is similar to wound shock but slower in development. It has been shown, according to this group, that there occurs a considerable fall in absolute plasma protein in association with hemoconcentration and that such cases are in the same need of plasma as wound shock cases. They feel that plasma is preferable to saline both in prevention and treatment of pulmonary edema. Their experience with the use of plasma, has not been great enough fully to assess its value, they admit, but its anti-shock property appears to be comparable to that of whole blood. They further feel that plasma is ideal for use in emergencies where no supply of blood is easily available and also in war surgery. The observation is made that the ideal plasma for administration is group AB(I) but the plasma of any group may be given to any patient up to 500 cc.

S. Levinson and associates(24) investigated the relative value of serum, saline, Hatmann's solution, and Hartmann's solution with glucose in dogs subjected to graded and repeated massive hemorrhage. They used dogs and each period of hemorrhage was followed by an interval of a half hour before infusing to duplicate the circumstances encountered in patients where a delay usually ensues following the loss of blood. A total of 80% of the calculated blood volume(7.5% of the body weight) was removed in stages of 30%, 20%, 20%, and 10% at approximately $1\frac{1}{2}$ hour intervals. One-half hour after each bleeding the animal was reinfused with an amount of fluid equal to

that removed. Due to dilution, only about 66 2/3% of the total
blood was actually removed in bleeding. When saline was used intra-
venously, they found that all animals derived only partial and tem-
porary restoration and that there was a progressive fall in blood
pressure, increasing acidosis, diminishing plasma protein content,
diminishing red blood cells and progressive state of shock terminat-
ing in death in all cases. With intravenous serum, the results were
strikingly superior and permanent; and the condition of the animals
was good at the end of the experiment. In this group, the blood
pressure was well maintained, the alkali reserve and plasma proteins
remained normal, shock was combated, and all survived. The red
blood cells were markedly diminished but none of the animals showed
any marked effects from this secondary anemia. They found that
blood was best but surprisingly only slightly superior to serum.
The animals receiving blood all showed only minor blood pressure
changes and weakness from the exhausting experiment. They state
that an important use for blood transfusion is in the treatment of
hemorrhage and that hemorrhage is often so rapid and severe that
prompt therapy is of vital importance to prevent severe secondary
shock. They are satisfied that studies have shown the essential
disturbance in massive hemorrhage is a decrease in the circulating
blood volume rather than the loss of red cells and that the immedi-
ate restoration of the circulating blood volume is the principal
need in treatment. These workers believe their work has shown that
serum overcomes all the effects of hemorrhage except the loss of
red cells and that this loss may be restored at leisure. That sal-
ine and other such solutions failed to accomplish the purpose is
evident in the transitory effect they gave. They feel the only

advantage of blood over serum is the red cell content of the former and that the disadvantages are the necessary careful preliminary typeing and matching of blood which is time consuming but necessary before transfusion. Saline or glucose have been used as an interval measure and are unsatisfactory if any degree of shock accompanies the hemorrhage; and acacia has the dangers of immediate reactions and delayed deleterious effects. The advantages of serum are that it can be preserved, it is ready immediately, there is no necessity for preliminary typeing, there is no likelihood of reactions and it is simple in administration. These workers conclude that serum should be the choice for interval intravenous fluid in this type shock but that it should not replace blood.

An interesting and well controlled experiment was done by Best and Solandt(25) who used dogs under intraperitoneal nembutal anaesthesia as their experimental animals. With blood pressure readings, cell volume determinations, and blood volume and serum protein estimations as their criteria, they produced histamine shock in one series of animals and traumatic shock both with and without extensive hemorrhage in a second series. There was some difficulty in evaluating the results because no two animals reacted in just the same manner but certain definite conclusions were drawn concerning the treatment of shock. They first found that shocked animals respond similarly whether shock is induced by histamine, trauma with extensive hemorrhage, or trauma without hemorrhage. Their results show that when the blood pressure was between 25 and 50 mm. of Mercury, the best form of treatment tested was intravenous pituitrin(single dose) followed by an adequate quantity of concentrated blood serum. If, some time later, the blood pressure

started to fall, this treatment was again repeated with benefit.
If the shock level was very low, they found that adrenaline may prove
more effective than pituitrin. When the pressure was from 50 to 20
mm. of mercury, serum alone was effective in treatment of the shock.
They further found that in traumatic shock, at least, concentrated
serum was more effective than isotonic serum. They have developed
a conception of shock that differs slightly from that found in the
preceding papers. Best and Solandt say that in severe traumatic
shock there is a decrease in blood pressure which causes a defici-
ent return of blood to the heart with a consequent further lowering
of blood pressure. The primary drop in blood pressure is due to
any one or a combination of the following: hemorrhage, fluid exud-
ation from atonic capillaries, and stagnation of blood in the dilated
capillary beds. The purpose of the adrenalin and pituitrin mentioned
above is to correct the vascular atony before administration of the
serum. In all three types there was found to be hemoconcentration,
and the blood protein determinations indicated an actual blood dil-
ution(as regards proteins) and a decrease in blood volume in shock.

Brennan(26) has made the first report on the results of a two
year investigation of plasma transfusion in the treatment of shock.
To date he has drawn conclusion from animal experimentation, 130
cases which were neurosurgical in nature, 56 cases which were oper-
ations associated with considerable loss of blood, and 21 cases in
which the results of plasma transfusion has been studied. He presents
some very interesting charts and concrete evidence of the benefit
of this last. On the surgical cases, serial red doll counts were
done every few minutes throughout the operations; and where possible,

blood volume estimations before and immediately following the operation were done. On the basis of these criteria, he felt that hemorrhage was associated with a rapid passage of tissue fluids into the circulation which causes a dilution of the blood. These fluids lack specific plasma proteins and some of the inorganic constituents of normal plasma. There occurs, therefore, a lowered osmotic tension so that fluid entering the red cells causes an increase in their size. Because of the decreased blood pressure and the increase in size of the red cells, the blood stream through the capillaries is slowed resulting in the closing off of some. These closed off capillaries then constitute storage cities for red cells. Brennan reasoned on this basis that plasma would serve as an autotransfusion, and he tried plasma in a number of patients. It is interesting to find that the plasma transfusions were followed by an increase in the red cell count and a return to normal of the mean corpuscular volume. This he attributed to the backwash of red cells out of the storage sites into the general circulation and has found that the cells reconstituted are equivalent to the number in one liter of whole blood. Brennan feels that these observations suggest a new form of autotransfusion for hemorrhage and that plasma, in these cases, should rival whole blood transfusions. I could find no confirmation of this work in the literature yet, and Brennan states that he is soon going to publish another paper along these same lines with a greater number of results in clinical patients.

After a survey of the literature, Elliott, Tatum and Nesset felt that animal experimentation had demonstrated that plasma and serum could be used as a substitute for whole blood. They therefore dispensed with animal experimentation and began using these

materials in patients on the basis of results obtained in the preliminary work of others.

In cases of shock without hemorrhage, they used plasma on the basis that plasma loss through atonic capillary walls into the extravascular spaces results in a decreased blood volume and hemoconcentration with consequent fall in blood pressure and anoxia. Although they have found blood to be a very satisfactory agent if available, Plasma has been used routinely in this type case for two years at Rowan Memorial Hospital. While it was difficult to compare the effect of different agents in different patients, they have concluded that plasma is no less effective than whole blood.

As regards shock due to hemorrhage, they feel that the shock is due to the anoxia caused by diminished circulating volume with the associated low blood pressure rather than to the decrease in red cells. They have found that if half of the blood volume is lost with a resulting red cell count of 2,000,000 R.B.C./cmm., there are still enough cells for oxygenation of tissues provided the pressure and volume are enough to circulate the red cells. It is therefore necessary to make early restoration of blood volume; and although whole blood is best, it is often not immediately availabe. In these cases, plasma, if given very early, nearly always make it unnecessary to give subsequent blood transfusions. The great advantage of plasma, was its immediate availability.

Best and Solandt reported on the use of concentrated serum in an earlier paper(25). In a later paper(28), they attempt to quiet discussion of the relative merits of serum and plasma as substitutes for whole blood. "In our more recent experimental work,

serum and plasma have been used interchangeably and the results
are identical. In employing these first to provide fluid and second
to provide serum proteins, which by their osmotic pressure attract
or retain fluid in the blood stream there is no significant diff-
erence between serum and plasma." This paper is a plea to prevent
discussion of the relative merits of the two from impeding the pro-
duction and inhibiting their use under appropriate conditions. These
workers will make a more complete report on the recent work they
mention.

The stability of serum and plasma and the growing body of evi-
dence(they abstract the work of Bond and Wright(18), Strumia(20),
and Levinson(22)) that pooled samples of these materials would be
used in human patients of any blood type stimulated these men to
reopen their investigations on the treatment with serum and plasma
of animals suffering from acute hemorrhage(29). Using the same tech-
nic described in a previous paper, they came to several conclusions
as regards acute hemorrhagic shock(posthemorrhagic shock). First
it was found that the longer the period between the onset of shock
and the initiation of treatment, the less effective was the treat-
ment. It was also found that 40% of the blood removed must be res-
tored to permit recovery and that comparable volumes of serum or
plasma gave equally satisfactory results. They feel that under the
conditions of their experiment, it is indicated that the volume of
red cells restored to the animal is more important than their oxygen-
carrying capacity.

A paper written on the treatment of wound shock(30) states
that the results of the investigations by American and British

clinicians and physiologists on shock during World War I and the
adherence to the shock theory of Cannon and Bayliss have been replac-
ed in the present World War by the concept of Blalock and others
who have shown that the loss of blood and blood plasma into the in-
jured regions is quantitatively adequate to account for the circula-
tory failure resulting from trauma to a limb, burns, and intestinal
manipulation. In Britain, the view is being accepted that hemorr-
hagic shock and traumatic shock are fundamentally similar, but it is
recognized that whereas hemorrhage is a relatively simple condition,
shock after extensive injury is a state resultant from many fac-
tors such as pain, exposure to wet and cold, fatigue, and dehydra-
tion. The Medical Research Council's first memorandum recently is-
sued has set forth the present status as regard the treatment of
these conditions. This memorandum lays greatest emphasis on the
importance of recognizing shock in its early stages and on the prompt
transfusion of blood, serum, or plasma in amounts sufficient to
restore to normal the blood volume. The report further states that
of all the measures in the treatment of shock, this last is the
most neglected and at the same time the most important. The British
feel, from practical experience, that early transfusion(before the
blood pressure drops to 90 or the pulse reaches 120 or over) must be
done if an effect is to be got. It is interesting to note that this
official communication did not differentiate or make a choice as to
the preference of blood, plasma, or serum in treatment of these cases.

Brown and Mollison of Britain(31) say, "the usefullness of plasma
and serum in the treatment of shock and even in acute hemorrhage is
now generally recognized." In their paper, they present evidence
that the serum prepared at the Medical Research Council's serum unit

is not toxic and that its administration in the case of shock is
successful. They have transfused 91 cases with this serum and remark
that one of the striking characteristics is the rapidity of increase
in blood pressure after the transfusions. In 80% of the cases, this
rise in blood pressure occurred within five minutes. It is their
custom to use the four-times concentrated serum in doses of from
40 to 500 cc.

The results of use of dessicated plasma in 45 cases of shock
have been reported by Hill and others(32) in this country. They
used the concentrated plasma in supplying 40% of volume lost(us-
ually 150-200 cc.), and found that it has in greater degree all the
desireable properties of isotonic serum and also other technical and
therapeutic advantages. In shock cases, there was an almost invar-
iable immediate, marked and sustained increase in the blood pressure.
They further found that other shock phenomena such as sweating show
dramatic changes after the administration of the plasma. Sweating
sometimes ceased entirely and return to consciosness from coma occur-
red often before all of a dose of the plasma was given. These work-
ers feel that although some of the rapidity of response may be due to
direct stimulation of the vascular system(?) most is due to the
proven rapid increase in circulating volume which is in turn caused
largely by the withdrawl of tissue fluid into the circulation as
was shown by the decrease in whole blood specific gravity, little
change in the patients' plasma specific gravity and the extent of
change in plasma volume. These were found to occur early after the
administration of the plasma. It was reasoned that since the eas-
ily utilized interstitial fluid amounted to three times the total

volume of blood plasma in a normally hydrated person, this source should be adequate except in severely dehydrated patients. It will be remembered that in a paper by other workers(26) there was reference made to the effect of the increase in size of the red cells in shocked patients. With regards to this aspect, these men state that hypertonic plasma should be more efficient than isotonic plasma in causing decreased red cell size by water shift. There was reason to believe that in sever posthemorrhagic shock, hypertonic plasma, by immediately accelerating the circulation, gave beneficial results when whole blood alone might have failed. In these cases, however, the plasma transfusion should be followed by whole blood. It was found that when the red cell loss exceeded 60% to 75%, no amount of plasma alone would suffice and that whole blood must be added for permanent good results. If the loss of red cells was less, it was felt that concentrated plasma might be used as a blood substitute to good advantage.

Hill etc. believe that the foregoing therapeutic advantages are largely due to the control of osmotic forces made possible by choice of concentration up to four or five times isotonic. The following indications are believed to be present in the use of the concentrated plasma: 1. the regulation of blood volume, 2. control of plasma protein levels, and 3. special adjustment of fluid balance when marked hypertonic effects are essential.

It is faulty literary style but not incorrect form in this type of paper to present at the last of a series of articles advocating the use of plasma the results of some work in which the use of plasma was found to be without benefit. In a series of nine

patients with severe hemorrhage from the stomach(33), it was found that plasma compared unfavorably with blood in its effect on the blood volume and the hemoglobin concentration of these patients. Plasm did not lower the degree of azotemia to the same extent as did whole blood and the general condition of the patients was adversely effected. It was thought that the forced dilution of the blood in excess of the limits within which blood dilution is favorable to recovery from hemorrhage was the cause of the ill effects from plasma. These men set a hemoglobin concentration of 50% as the lower limit beyond which the use of plasma in post hemorrhagic shock is contra-indicated. Further support of these results will be mentioned in a paper abstracted under the heading of Blood Transfusion.

As was the case in presenting the work on shock, the leading paper in this series on burns is one which will present the pathological findings as a means of review and orientation for the experimental and clinical findings which will follow.

In 1936, Weiner and others(34) did some work with the purpose of showing the significance of loss of serum protein in the therapy of burns. They know that large amounts of blood plasma are lost into the burned areas from the experimental work of others; and they knew, as is generally recognized, that this was the prime, if not the only factor in hemoconcentration.

For their determinations, they worked with 40 patients all of whom were victims of severe burns, some causing death. They estimated the blood concentration roughly by means of red cell counts and found there was a rapid (often within one or two hours) increase in red cells up to 6,000,000. In two cases, the count was as high as 8,000,000. The viscosity of the blood was so great in the severe burns that they were unable to obtain blood by venipuncture of even the large veins. In spite of the hemoconcentration, it was found that the serum protein of such blood was normal or low soon after admission. The amount was 7% or less in all but one case and the usual figures were between six and seven percent. Comparing this with the 10% or more which follows blood concentration due to extreme dehydration from vomiting, diarrhea, etc, they felt that these figures were indicative of an actual or a relative loss of serum protein.

In the patients treated with saline and glucose in large amounts, there was a fall of serum protein and no corresponding decrease in the red cell count signifying that there was no correction of the essential hemoconcentration. In these cases, the A/G ratio was usually between 2.9 and 3.2 and the return of serum protein to normal required weeks. In addition to this, there was subcutaneous edema of the unburned skin when five to eight liters of the fluid was given daily, and the kidneys often failed to secrete over 10% to 20% of the fluid given.

On the other hand, the patients receiving plasma or acacia showed a rapid decrease in the subcutaneous edema. The hemoconcentration in these cases rapidly diminished; and in some, the red cell count dropped in four to eight hours after the administration of 500 to 1000 cc. of acacia or plasm. These men feel that these results were comfirmatory evidence that the loss of serum protein is a severe complication of severe burns and that the store of body protein is not sufficient to restore rapidly this loss when water, glucose and electrolytes are administered. They believe that severe burn cases require large amounts of protein and that the injection of plasma is more efficacious than whole blood because of the extensive hemoconcentration. In addition to relieving the hemoconcentration and elevating the serum proteins, plasma may aid in the resistance to infection(there was no basis for this in the results found). As was seen above, the use of saline solutions caused a generalized edema, and, they believe, a decrease in the tissue resistance. Weiner and associates further suggested that it is possible that the process of protein replacement would be enhanced by

the dietary administration protein such as beef protein, soy bean
meal etc. which are rapidly converted to blood protein.

McClure(35), in a discussion of the treatment of the patient
with severe burns states that the lethal factor in such cases has
not been definitely established. Although some feel that there is
a toxin formed in the burned area from which absorption occurs with
consequent distribution throughout the body by the circulation to
produce the systemic effects, a meeting of the French Surgical Con-
gress found that all agreed on the great importance of the loss of
plasm protein. Other factors to be considered in the cause of death
in these cases were liver damage, anoxia, etc. McClure states that
hemoconcentration is the essential chemical pathology in severe
burns and that cases receiving fluid have still progressed to death.
He believes that serum transfusion promptly replaces the large
amount of circulating protein that is lost in severe burns and that
water and saline are worse than nothing as regard therapy. He feels
that the hematocrit determinations and serum protein determinations
at frequent intervals are better criteria of effect than the blood
pressure record.

At Henry Ford Hospital, they have divided the treatment of the
burn patients into local and systemic measures. Among the sys-
temic measures are the restoration of fluid balance by 5% dextrose
and saline to give a 1500 cc. 24-hour urine output, blood plasma
transfusion when the hemoglobin is 15.6 grams or over, and blood
transfusion in the secondary anemias.

A difference of opinion is found in reading the results of ex-
perimental work on dogs by Trusler, Egbert, and Williams(36).

They have come to feel that the tannic acid theory of the treatment of burns is fallacious and there is no local application that can be expected to save a life after a severe burn (this last was not claimed by the originators of the tannic acid treatment by the way). They have developed the idea that the cause of death in extensive burns is shock and that the shock can be divided into two phases; 1. the traumatic phases in which the causitive factors are blood stasis and the loss of blood plasma which escapes into the tissue through the capillaries injured by heat, 2. the inflammatory phase was found to be a complex situation in which the loss of fluid was accompanied by the other morbid processes of diffuse thermal inflammation. This last was supposed to account for the toxic manifestations in the burn cases. They found that the persistent forcing of water by mouth might lead to fatal water intoxication and their explanation was on the basis of disturbed physico-chemical relations of the blood. On the basis of their work, they say that blood transfusions should be given early and repeated frequently throughout the self limited period of the shock reaction. They also say that other fluids should be given in moderate quantities and that large amounts of dextrose are indicated. It should be noticed that in one of their cases rapid recovery was found to occur following six large blood transfusions in four days. However, because of the polycythemia, citrated plasma was given. It seems to me that these results would be more acceptible if they had compared the effects of blood and plasma and recorded the findings of plasma protein determinations, blood concentration readings, and correlated these with clinical improvement. It seems that the crux of the effect in these cases was the administration of fluids with the

blood which would tend to avoid further hemoconcentration which has been found to occur in burn cases by so many other workers.

Elman draws conclusions as regards burn therapy from an extensive clinical experience and presents the results of therapy in five cases in a recent paper(37). In 1935, following a sewer explosion 40 patients with severe burns were admitted to his service, and in every case, there was found a relative as well as an absolute fall in the concentration of the serum proteins. It was found that if the manifestations of severe burns were combatted promptly, many lives could be saved. The manifestations were found to be largely due to loss of tissue and especially the plasma proteins, and the replacement of the latter by plasma transfusion was essential to maintain the circulation and to reduce the concentration of the blood. It was his experience that the plasma loss was of the extent that it was necessary to give 10 cc. of plasma per kg. of body weight, and this was repeated in several instances. Elman advocates a high protein diet but believes the intravenous use of amino acids awaits further clinical trial. He says that a single injection of acacia may be used if no blood is available, but it is greatly inferior to plasm. It is his opinion also that saline or glucose infusions are not only ineffective but also harmful. He mentions that the increase in urinary nitrogen in severe burns is evidence of protein destruction.

Elkington, Wolff, and Lee have given this subject much thought and have reported on a series of cases in a paper(38). They repeat that it has long been known that a decrease in the fluid portion of the blood(hemoconcentration) is a common phenomenon in severe burns. They list the step by step gain in the knowledge of the pathology

and treatment of severe burns--Baraduc(1862) described the thickening
of the blood and suggested restoration of the fluid portion of blood,
Davidson(1927) found a moderate lowering of the plasma protein con-
centration in the more severe cases, Underhill(1930) showed that
the capillaries in the burned area were permeable to methylene blue
and that a burn covering 1/6 the body surface resulted in a local
edema fluid equal in quantity to 70% of the total blood volume.
Blalock showed that the edema fluid and plasma were nearly identical,
and many have recently shown the decrease in the plasma proteins.

Elington etc. studied some burn cases in the light of the find-
ings I have listed above and in view of the more recent findings of
other workers. They confirm the finding that fluid imbalance is
primarily due to an altered capillary permeability with a shift of
fluid and protein into the tissues rather than to the outside.
Their studies indicated that the mechanism of fluid imbalance is set
into motion during the first few hours after a severe burn and that
capillary stasis and altered permeability in the burned area per-
mit passage of plasma proteins across the capillary membrane with
a corresponding disturbance of osmotic pressure. Secondary to this
change, tissue fluids are increased and the plasma volume is dimin-
ished so that the fluid imbalance is primarily an abnormal distri-
bution or shift of fluid. They reasoned that the fluid lost from
the vascular compartment would best be returned by replacing the
lost plasma protein which would in turn raise the plasma osmotic pres-
sure to a value sufficient to restore and maintain the normal dis-
tribution of fluid between the intravascular and interstitial com-
partments.

There were two unknown factors pertaining to the restoration of plasma protein; 1. the time at which the capillaries in the burned area regained their impermeability to protein and 2. the total quantity of protein required. Their work indicates that the loss of plesm protein continues until the 31st to the 40th hour; and that during this time, excessive hemoconcentration may be prevented by small repeated plasma transfusions. They were unable to say whether or not this period of healing was a general biologic property of damaged capillaries. They corrected the deficit of plasma protein after the capillaries had regained their impermeability(40t hour) by a large plasma transfusion. The second unknown factor mentioned above was satisfied by calculating the amount of protein required by a formula based on hematocrit values, plasma protein concentration, and the body weight. Their method restores the plasma volume to normal without the administration of excessive amounts of protein-free fluids(water and electrolytes) which they believe are needed only to small degree because the excess fluid in the tissues should be available when plasma osmotic pressure is restored to normal. They feel, as do several other workers already mentioned, that the administration of normal saline only increases the edema already present and water may cause a dangerous lowering of the extracellular electrolyte concentration due to interference with normal renal defense by diuresis secondary to lowered plasma volume and plasma protein concentration.

In Elliott's work already mentioned under shock(27), it was found in clinical cases that following burns there is exudation of fluid of high protein concentration. They have constructed a chain

of events to explain this situation. The local capillary damage results in increased permeability to proteins and the release of "H" substance which, in turn, produces a similar capillary change throughout the body. The resulting loss of plasma proteins is the basis of the decrease in blood volume, hemoconcentration, and circulatory failure. While they realize that whole blood transfusions has been known to be beneficial, their results show that plasm is so effective that the transfusion of whole blood in the presence of hemoconcentration is contraindicated when plasm is available.

The British have found that war burns, as might be expected, bring special problems in treatment(39). These patients reach the hospitals, for the most part, in the late stages; and 60% of the deaths are direct result of secondary shock. From clinical and laboratory measurements, they have found that shock is primarily due to loss of plasma protein and the destruction of tissue protein. Hemoconcentration is the rule, and blood transfusion is not required unless hemorrhage has occurred. They feel that after morphine, hot fluids by mouth, external heat, and oxygen have been administered, the most valuable therapeutic agent is transfusion of plasma.

Black of England has reported on eight patients with severe burns or scalds of whom seven were treated with plasma or serum or both. The report was well investigated as regard laboratory findings. Before treatment was begun, there was found an increasing shock with the classical symptomatology, progressive hemoconcentration, low plasma chloride and bicarbonate with a normal urea. There was also a fall in the plasma volume and in total plasma proteins although

the protein concentration was often high. The serum sodium was low, the serum potassium high, and plasma protein equivalent to 1/4 of the total was found to have been lost in most instances within a few hours. On this basis both concentrated and isotonic plasma transfusions were tried. The infusions were followed by a rise in plasma volume as well as a striking clinical improvement. Of the two types of plasma, the isotonic was found to give the most satisfactory results.

There is much work being done on the use of plasma and serum in therapy of burns. The foregoing papers were chosen as a survey rather than an exhaustive review of the literature, and an attempt was made to avoid choosing work with duplicate or too similar findings.

NEPHROSIS :

The nephrosis refered to here is the true of lipoid nephrosis.
Cecil(41) defines it as a chronic disease of variable duration in
which the nephrotic sydrome exists without evidence of glomeru-
lonephritis or amyloid disease, occurring more frequently in children,
having both a good prognosis and spontaneous remissions, and char-
acterized by an albuminuria associated with a depletion of plasma
albumin. Cecil further states that the studies of the blood in
these cases uniformly show a low total serum protein content(us-
ually below 4%) and partition of these proteins reveals a relatively
greater reduction of the albumin fraction. So much for the review
of this syndrome.

Aldrich and others(42) noticed in the Childrens' Memorial Hos-
pital that nephrotic patients who had pneumonic peritonitis as a
complication had a diuresis following the use of convalescent soar-
let fever serum in 100 cc. doses. This observation coupled with the
fairly recent realization that in nephrosis, the kidney need not be
severely or irreparably damaged and that even in the stage of great-
est disturbance in water excretion, tests for renal function may
give approximately normal results suggested the possibility obtain-
ing a result from treatment directed at the associate pathology
rather than at the kidney.

With this thought in mind, they tried injecting four-times con-
centrated human lyophile serum(pooled) and obtained blood protein
values before and two days after the injections. They injected
nine patients with typical nephrosis all of whom were in the edem-
atous phase and obtained a complete and immediate diuresis in six

cases. Of these, four patients not only lost their edema but had a normal urine within a few weeks of the injection and were clinically well at the time the report was made. One patient of the nine had a delyed and incomplete diuresis, and two patients showed no beneficial results. It was found that the patients with a favorable response lost weight in a way similar to that in which weight is lost in a spontaneous renal orisis. For this reason, it was felt that the serum initiated some physiologic response rather than merely replacing the serum proteins. These workers acknowledge that diuresis could have been coincidental with a spontaneous renal crisis but believe that it was most fortuitous that serum had been injected on the day before the diuresis. The apparent failure of the serum in three cases was thought to be due to the severity of the condition, inadequate dosage, or unknown complicating factors; and these workers feel that their results are only indicative of the need for further investigation as regards the physiologic mechanism involved and the disage standardization.

The report above is obviously the basis for a similar study done by Jeans at Iowa State. He repeats the generally recognized fact that a low blood protein is one of the characteristics of nephrosis and believes that some relationship exists between the level of blood protein and the amount of edema. He reasoned that one therapeutic objective should be the raising of the blood protein above what he terms the critical level for edema. Although repeated blood transfusions are moderately effective in raising and maintaining the serum proteins, there is eventually a relatively more rapid increase in the red cells than in plasma proteins because of the continual

46.

INTESTINAL OBSTRUCTION:

Fine and Gendel have done some excellently controlled experimental work on the use of plasma in intestinal obstruction(46). They used dogs under intraperitoneal nembutal anaesthesia after a starvation period of 24 hours. They then ligated the pylorus and divided the bowel at the ileocecal junction. A glass cannula was inserted into the proximal end of the divided intestine, brought through a stab wound in the animal's abdomen, and connected with a pressure bottle. By means of this arrangement, the bowel was distended with air under a pressure of 20 cm. of water which is the pressure commonly found in clinical obstruction. Using the normal blood volume and plasma volume determinations as a control, they made interval determinations of the blood volume and plasma volume while the animals were obstructed and distended and while they administered plasma and saline intravenously.

In previous studies of intestinal obstruction, it has been shown that the loss of blood, fluid, and electrolytes into the intestinal lumen, bowel wall, and peritoneal cavity were not responsible for the loss of plasma or for the rapid death that occurs in obstruction with distention. The possibility of noxious nerve stimuli originating in the distended wall acting as the cause has also been eliminated. Although they have no experimental evidence to prove the point, these workers believe that part of the lost plasma is forced into the interstitial spaces of the pelvis and lower limbs because of the impeded venous return from these areas.

They found that plasma loss continued as long as the bowel was distended in this experiment. The extent of the plasma loss, un-

less compensated, was enough in itself to cause death of the animals. They felt that this loss was one of the primary considerations in the pathologic physiology of this type situation. After trying intravenous administration of saline and plasma, it was found that physiologic saline even in amounts more sufficient to compensate for the fluid lost conferred no beneficial effect. On the other hand, the injection of plasma in amounts sufficient to compensate for the lost fluid in the experiment conferred a protective influence and markedly prolonged the life of the animals.

At a later date, Fine and Gendel reported on the effect of acute intestinal obstruction on the blood volume and plasma volume(47). They used 18 dogs and their obstruction procedure was the same as the method described above. They determined the normal blood plasma volume and calculated the blood volume one week before the experiment. After distending the intestine, they found that the distention alone did not result in the loss of fluid into the intestinal lumen, bowel wall, or peritoneal cavity. However, distention of the obstructed intestine resulted in an early and progressive loss of blood plasma(31.4% in 4-6 hours and 55% in 24 hours). The dogs with simple obstruction died more slowly than did those with a superimposed distention, and death was even more rapid if strangulation and distention were both produced. In the latter, a 48% loss of plasma occurred in four hours. From these results it is obvious that there is need for immediate decompression in these cases. These workers feel there is as much indication for immediate administration of plasma in sufficient amounts to restore the normal plasma volume and that this amount is greater than that usually given in

clinical cases. They think better results can be obtained by using the hematocrit as a criterion of the need of plasma or whole blood and by giving the plasma before evidence of shock is indicated by the blood pressure determinations.

In a more recent report, these same men have confirmed some of their own results and investigated the problem further(48). This time, they found that plasma loss was directly proportional to the time that the gut was distended. This loss of plasma continued as long as the obstructed small intestine was distended and was sufficient to cause death of the animals unless corrected by plasma administration. They again found the administration of saline ineffective in prolonging life in these animals and explained that death was not due to dehydration and dechlorination in their obstructed dogs. Aside from the confirmation of the effectiveness of plasma injection, there was little else found that has not already been mentioned in the preceding reports.

The use of plasma seems to be a relatively recent measure as regards intestinal obstruction. Very little has been done on this subject; and for that reason, it has been necessary to consider the reports of only one group of workers.

INCREASED INTRACRANIAL PRESSURE:

One of the first reports on the use of serum for the treatment
of increased intracranial pressure is that made by Hughes, Mudd, and
Strecker(49). They treated ten patients having increased intracran-
ial pressure with four-times concentrated human lyophile serum.
To determine the results, they followed the cerebro-spinal pressure
changes by means of lumbar puncture readings for a period of one
hour following the injection of the serum. The usual dose was 50
cc.

It was found that unless the rate of injection was slow, there
was a rise in cerebro-spinal pressure following which the pressure
decreased to its point of greatest reduction in about 30 minutes.
The pressure readings then fluctuated about that level for a period
of one hour(not measured after this period except in one patient).
In nine of the patients, there occurred an increase in the pulse
rate and in the blood pressure readings following the injection of
the serum. The increase in systolic pressure varied between 20 and
58 mm. of mercury.

A typical course is that of one patient who showed an initial
cerebro-spinal pressure of 450 mm. The injection of 50 cc. of ser-
um was followed by a decrease in pressure to 165 mm. in 30 minutes
and a rise to 300 mm. at the end of an hour. At that time, a sec-
ond injection decreased the pressure to 210 mm.; and the reading
was 240 mm. at the end of six hours(only case measured after a period
of more than one hour). This represented a decrease of 210 mm. un-
der the initial pressure. These men believe that this type serum
is very effective for dehydrating the brain and that the increase

in blood pressure following the injection is of additional benefit in cases of increased intracranial pressure accompanied by shock. They feel that the method is superior to the use of magnesium sulphate or glucose solutions because the serum consists largely of protein and cannot diffuse readily out of the blood vessels after intravenous injection. This results not only in an increase in the osmotic pressure of the blood but also in maintenance of this increase over a long period of time. There was no reaction following the slow injection because of the high dilution that the serum undergoes when it is introduced into the blood stream.

A critical review of the report raised some interesting questions. Fremont-Smith agrees that the great advantage of serum in brain dehydration is the length of time that the protein remains in solution, but asked if the continued decrease in spinal fluid pressure could not have been due to the leakage of fluid through the hole in the dura made by the spinal puncture. It was also brought out that the increase in blood pressure might have a tendency to increase the bleeding in concussion.

In another report at a later date, these same workers rewrote the above findings and made several other observations(50). They found that comparative studies showed the concentrated serum to be more effective than sucrose in decreasing the cerebro-spinal pressure for long periods. The usual duration of effect with sucrose was seven and one half hours, and the duration of effect with serum was 20 hours. It was suggested that the serum be dissolved in water rather than in sucrose(as had been suggested by others) because of the great viscosity resulting from the latter. Hughes etc. also

cautioned against giving serum to patients with food allergy because of the food proteins present in the serum.

Because of the criticism of technic, Wright, Bond, and Hughes again worked with the concentrated serum under more accurately controlled conditions(51). They used dogs under sodium amytol anaesthesia this time and recorded the cerebro-spinal pressure continuously after cisternal puncture. The pressure observations were made over a period of two hours after the anaesthesia was given and before the injections were made. Four-times concentrated serum was used.

Their results showed a fall in the cerebro-spinal pressure following the intravenous administration of serum. By varying the dosage, they found that larger doses gave not only a greater drop in pressure than did the smaller doses but also a more prolonged effect. Eight cc. of serum per kg. of body weight maintained a reduction in the pressure for over 20 hours. Compared with this, similar doses of concentrated saline solution decreased the pressure for only two hours.

MISCELLANEOUS:

As early as 1935, it was found that foreign plasma protein was not utilized in the body economy when introduced parenterally into a protein-fasting dog(52). Dog hemoglobin given parenterally did not keep dogs in nitrogen equilibrium, but dog plasma maintained a protein-fasting dog in nitrogen equilibrium. At that time, therefore, it was believed that there was a contribution from plasma proteins to body proteins.

By 1939, the use of plasma was definitely on the upswing. Elkington and others(53) introduced the idea that electrolyte and water balance in surgical patients could be evaluated fairly accurately by simultaneous determinations of hematocrit value, plasma protein, chlorides, and carbon dioxide combining power. Hemoconcentration, as shown by a rising hemotocrit or plasma protein value was considered to be an indication of extracellular water; and a low or falling hematocrit value indicated the need for whole blood transfusion. A low protein concentration indicated there was a prime need for plasma transfusion when the hematocrit value was normal or above normal(as in burns). In this protein was supplied without adding red cells to a vascular system already overloaded with them. In this report, cases cited for plasma transfusion were as follows: protein loss(infection, ascites), protein loss plus hemoconcentration(burns, peritonitis), and following a cecostomy or gastroenterostomy.

One worker (54) says that the indications for the use of plasma transfusions are rapidly becoming broader as appear to be supplanting the giving of whole blood in many instances. He reviews the effect of concentrated plasma on increased intracranial pressure and is of

the opinion that plasma is better than blood in shock except where hemorrhage is the cause of shock. Other indications for plasma are listed as follows: cachexia, malignant tumors, G. I. surgery with complications, unresolved pneumonia etc where blood protein levels must be sustained or replenished.

In recent years, the intravenous use of blood plasma in the place of whole blood has been made the object of intense study by the staff of the Bryn Mawr Hospital(55). They have used both serum and plasma in infections, in the prophylaxis and treatment of nutritional hypoproteinemia and the anemia resulting therefrom, in burns, in hemorrhagic and hemolytic diseases, in pre-eclamptic states, in liver disease, in chronic colitis, and in secondary shock. It will be interesting to read a report on the effect of plasma transfusion in these cases if someone has the courage to make it. The purpose of the discussion in this case was simply to emphasize that the intravenous use of citrated blood plasma without cross-matching is both safe and convenient whether the plasma is fresh, preserved by refrigeration, or obtained by the loyphile process. They have, however, had reactions with lyophile serum and think they may be due to fibrin precipitation in preparation.

Another group(56) has reviewed the literature in the past five years and found that plasma and serum is usually preserved by drying and is apparently preserved indefinitely to be redissolved and used in a dilute or concentrated form. The advantages of serum and plasma over blood are listed as easy availability, excellence of preservation, ease of transportation, and convenience of administration. They feel that plasma transfusion will become an important

part of intravenous therapy but fear that the indiscriminate administration in large quantities without regard to blood groups may result in dangerous reactions. Wangensteen has done some work on the administration of bovine and human plasma to man(57). He used plasma in preparing patients with carcinoma and obstruction at the gastric outlet for surgery. All were essentially afebrile and showed the effects of hypoproteinemia. During the study, the patients were on a protein-free diet and were given carbohydrates to provide 1200 Calories daily. Daily urinary total nitrogen determinations were made as were also the N.P.N., urea nitrogen, and sugar. Interval studies of plasma proteins, blood N.P.N., blood urea nitrogen, and chlorides were done. They allowed the patients' excretion of nitrogen in the urine to reach a basal level while being supported with carbohydrates. In this way, the effect of the administration of human blood, plasma or bovine plasma on the nitrogen excretion could be followed. It was found that human plasma given intravenously was retained and utilized. One patient to whom a daily average of 450 cc. of plasma was given over a five day period was maintained in nitrogen balance. In starvation states, human plasma was found to be superior to blood for maintaining nitrogen equilibrium. It was found that bovine plasma could be given ot humans in fairly large quantities and was apparently utilized but before these workers are willing to recommend it, they prefer waiting on further study as regards safety of administration.

The report on work done by Elliott and others has already been mentioned(27). They have found that plasma transfusion is of definite aid in clinical patients after abdominal surgery who not only

are unable to take protein by mouth but also lose it through the kidneys and from drainage. They feel that other cases requiring plasma are losing protein because of fever, infection(tissue destruction), and certain kidney lesions. In hypoproteinemic states secondary to starvation and loss of protein over a long period of time there is an indication for plasma transfusion. In their experience, a plasma protein of 4% or less is associated with edema; and oral protein along with intravenous plasma result in a dramatic clearing of the edema. In a series of 445 plasma transfusions, they have had only three reactions which were later found to be due to something other than the plasma itself.

Levinson and Cronheim have studied the suppression of iso-agglutinins by serum(58). Their experiments demonstrate the agglutinin neutralizing action of serum and also of body cells. This mechanism provides a wide margin of safety in protecting the recipient's red cells from the infused agglutinins and explains the practibility of using universal donors and the safety of plasma transfusions without preliminary blood grouping or compatibility tests. They recomment that serum or plasma prepared for transfusions be made up of pools containing all blood groups to give a final low agglutinin titer fluid.

There has been much discussion as regards the use of plasma or serum in hemorrhage because of the supposed inadequacy of these substances in aiding the clotting of blood. After describing the usual advantages of plasma and serum over blood, one British worker says, "-----the recipient's own clotting mechanism is sufficient to stop hemorrhage when serum is used.

I have saved until last in this series a report of an experiment done not too recently but showing several indications for plasma transfusion in the surgical field. This work was done by Harkins and Harmon who found that a plasma-like fluid was lost from the blood stream in several conditions including burns, freezing, bile peritonitis, tissue autolysis in vivo, acute pancreatitis, pneumonia and pulmonary edema, intestinal manipulation, portal and mesenteric obstruction, externally strangulated colostomy loops, and release of constriction of an extremity. They worked on dogs at a time when it was first being generally recognized that the fluid leaking out of the blood stream in the conditions listed was more like plasma than blood. They found that the loss of the plasma was rapid(occurring in several hours) and that the loss of less plasma than whole blood could be tolerated in animals before death occurred. It was found that the amount of plasma-like fluid lost in the above conditions approached that which would produce death when removed experimentally by plasmphoresis. They have some tables of the results of these conditions on the blood protein, percent of increase in hemoglobin, and the hematocrit increase. This last is the interesting portion of their work. Although they did not correlate these three factors, it can readily be seen that by so doing, an indication as to whether blood or plasma transfusion should be given will become apparent. As a matter of fact, some of the most recent findings in clinical cases of shock are related to the size of the red cells and the above relationships; and the failure to recognize this amounts to a loss of eight years of progress in this phase.

BLOOD TRANSFUSION:

One is left rather bewildered after reading the indications for blood transfusion listed in a surgery textbook(61): "Blood transfusions are of value to make good the deficiency of blood after acute hemorrhage, to increase the coagulability of the blood by supplying fibrogen, to make good a deficiency of red cells, to furnish substances in which the blood is deficient, such as antibodies in acute infections and functionally active hemoglobin in carbon monoxide poisoning, to act upon the bone marrow which is disordered, as in leukemia, to dilute toxins in toxemia, and to increase the bactericidal power of the blood through the action of leukocytes and the opsonic power of the serum." In order to show the prevalence of transfusions in one large clinic, the figures on Mayo Clinic can be cited. In 1939, 3723 transfusions were given. Of these, 12.9% were received by children of 15 years of age or under, and 26.7% were in non-operative cases. In the surgical cases, 7.6% were preoperative, 13.7% were operative, and 51.9% were postoperative. Since 1937, they have been using more and more refrigerated blood until 1939, during which they used fresh and preserved blood in almost the same number of cases. With these figures in mind, it seems one should have a better idea of the indications for transfusion. Because transfusion is now a relatively old procedure, the boom of experimentation is over and most papers represent the opinions of various men who have clinical experience as the basis of their opinions.

In a symposium on transfusion, DeBakey and Honald(63-64) have said that in conditions where there is depletion of the vascular tree (shock), blood causes a retention of fluid in the vascular tree and

its colloid and electrolyte content maintains the normal osmotic tension. For this reason, one of the main effects of blood is its substantial increase and maintenance of fluid in the vascular tree.

It has been clinically and experimentally demonstrated that addition of blood by increasing the oxygen-carrying power is of benefit in patients with primary or secondary anemia. It has been found that there is a hemostatic effect when blood is given in the hemorrhagic diatheses.

In hemorrhage or loss of blood from any cause, blood is the only substance that can relieve so adequately and physiologically the manifestations of blood loss. These properties along with the hemostatic influence of blood have made hemorrhage the chief indication for transfusion. The mechanism of effect is immediate restoration of intravascular bulk and oxygen-carrying power. Incidentally, DeBakey includes bleeding peptic ulcer cases in this category.

Because they feel no other procedure can so effectively combat shock, blood transfusions are almost routine following prolonged or severe operative procedures at Tulane Surgery.

From this point on, the assertions of beneficial effect are not quite so positive. Thus the effects in hemorrhagic purpura are found to be variable, and blood has been given in the past on the assumption that it supplies substances necessary for the normal process of coagulation which may be deficient in this condition. In a similar way, blood has been used in hemophilia with results that vary according to the reports made. It is their opinion, that hemophiliacs should receive blood in any surgical procedure regardless of its extent.

Success has been frequent enough in hemorrhagic disease of the new-
born to warrant transfusion in these cases. A similar standpoint
is taken as regards cases of hemolytic jaundice, aplastic anemia, and
acute hemolytic anemia. They beg the question as regards results in
infection and have had no success in cases of leukemia. In cases
of poisoning with carbon monoxide, nitrobenzol and benzol, where the
hemoglobin combines with the intoxicant to form a stable compound,
blood is beneficial through adding red cells capable of oxygenation.

In a review of the literature on blood transfusions from 1934
to 1935(65), Douglas has found blood is being used to increase the
circulating volume, to add living red cells as oxygen carriers, to
add platelets and plasma proteins, to add prothrombin, and to
aid hemostasis and add immune bodies. Hemorrhage has been and still
is the prime indication. In gastrointestinal hemorrhage, Filatov
has reported recovery of 84% if transfused before shock sets in and
40% if transfused after shock sets in. It seems that this type
case is becoming more an indication since drip transfusion has been
popularized.

He found that blood is being used in shock and in burns but
that the use of plasma and serum is being tried with good results.
At the Mayo Clinic, 70% of transfusions are preoperative and post-
operative measures. At Tulane, 60% of transfusions are these; and
at the Cleveland clinic, this is a routine procedure. In thrombo-
penic purpura, whole or citrated blood(but not preserved blood) is
being used. Blood is often the only means of stopping hemorrhage
in hemophilia he found. Hemorrhagic disease of the newborn is still
being effectively treated by transfusion as were jaundice cases until

vitamin K was discovered. In these last cases, blood is generally considered to still be a good treatment.

As regard the anemias, blood is of course being used. It is needed to tide hemolytic jaundice(familial) paients over a hemo-clastic crisis and to prepare them for splenectomy. Lederer has shown that a single transfusion usually cures acute hemolytic anemia. Most report success in treatment of icterus gravis neonatorum, and one worker has come to believe that blood is a specific in these cases. Only transfusions can keep the aplastic anemia cases alive until spon-taneous recovery occurs. Blood is still being used in pernicious anemia until liver can become effective.

Most reports indicate that blood is of little if any benefit in cases of leukemia and agranulocytosis. Immunotransfusion is still too new to be evaluated finally, but seems to be most effective when there is an associated anemia or in cases of infection with hemo-lytic organisms.

Norcross(66) believes there are six main types of deficiency that are best treated by blood transfusion. The first is deficiency of whole blood which is present in acute hemorrhage and in that type of shock in which the normal blood volume is no longer sufficient to sustain life because of the pooling of blood in the large dilated capillary beds. The second is a deficiency of red cells such as is found in chronic anemias. He believes blood greatly helps these cases and has found that a 500 cc. transfusion will give an increase in hemoglobin of about 2 Gm. per 100 cc. The third is a deficiency of hemoblobin without change in the number of red cells(as in carbon

monoxide poisoning), and the fourth is a deficiency in white blood cells. To save repetition, it can be said that his views regarding these indications are the same as have been found in the reports already discussed. The fifth indication is a deficiency of platelets as is found in the acute stage of thrombocytopenic purpura where transfusion will carry the patients through the acute stage until permanent therapy can be instituted. The last indication seems to me to be a waste basket and the information is not of any value.

In a symposium on transfusion, Forkner(67) has essentially the same ideas that have been already discussed. However, he feels that transfusion is not indicated unless other measures have failed in a slowly developing anemia until a level of 2,000,000 red cells or 5.5 Gm.% of hemoglobin is reached. The only additional information is that given by Smith in the same series. He has found that infants with severe malnutrition and reduced blood volume and serum proteins show pronounced improvement with blood transfusion. Other indications he named were conditions associated with the anemia, the toxemia, and the metabolic disturbances related to malnutrition and dehydration in infants.

The status of blood transfusion in the southern sections has been reported by Payne(68), and is found to be identical with those listed in the foregoing reports. The same is true of the report by Cooksey(69) with one exception. He has found that the acute hemolytic anemia that sometimes follows the use of sulfanilamide requires an immediate transfusion. He also found immunotransfusion dramatic in its effect in two cases of brucellosis and one of hemolytic strep tococcus infection.

Burton(70) says most surgeons agree to the following indications for blood transfusions: to replace a dangerous loss of red cells, to restore blood volume in secondary shock, to confer, increase or activate immunity reactions, to stimulate blood production in anemia secondary to sepsis or trauma, and to obviate or reduce shock in long surgical operations. He says that the majority of acute traumatic anemia cases will die unless a large and immediate transfusion is given and that cases of profound secondary shock with considerable external loss of blood are nearly as urgent. He very cleverly points out the difference in these two conditions when he says that in shock the red cells are in the wrong place and in hemorrhage they are gone for good. In line with the work on plasm administration is his opinion that in traumatic injuries where shock is profound but loss of blood slight, blood has no advantage over other solutions. There experience has shown that blood transfusion should be avoided in the reaction stage following shock because of the chance of producing rather violent reactions(in line with serum?).

In reviewing a large number of peptic ulcer cases with hemorrhage in Bellvue Hospital, Hinton has approached the question of transfusion very logically(71). Ten percent of cases did not respond to medical care and operation during the acute stage constituted a life-saving measure. He feels that when the blood pressure has fallen to 80/60, the red cell count to 2,000,000 or less, the hemoglobin to 35% or thereabouts, it is obvious that the patient needs support in the way of transfusion. It is their practice to let this measure be a lead as to whether to continue conservative measures or operate. If, after a 500 cc. transfusion has been given,

the red cell count, hemoglobin and blood pressure remain low, it is assumed that a large vessel has been eroded. If these conditions still present after the procedure is repeated, they have found it conclusive evidence that delay in operation may prove fatal.

In an extensive and complete discussion of blood transfusion, Vaughn mentions that the chief value is its immediate effect in increasing blood volume, plasma proteins, hemoglobin concentration, blood platelets, and other factors concerned with the clotting mechanism(72). In Britain, the chief need for blood is in patients with recent severe blood loss. In such cases, the indications for transfusion may be clinical only(restlessness, pallor, dyspnea, systolic pressure of 70 or less, and rising pulse rate) because the red cell count and hemoglobin may be normla or hypernormal due to concentration of the blood. They have found also that blood seems to be of value in patients with prolonged sepsis and anemia such as are found in cases of gunshot wounds that failed to heal readily.

As regards surgical procedures, hemorrhage and shock are considered to be the most dangerous complications requiring blood transfusions according to Raudenbush(72). In his report of series of cases, he attempts primarily to show that venoclysis is safer than blood improperly prepared; but at the same time, he feels that blood, being the normal fluid of the human body is the ideal agent to infuse into the circulation to replace fluid and volume and restore functions dependent on this replacement.

It has been the experience of Douglass and Laughlin(74) that patients with resistant forms of pyelitis during pregnancy almost always

have a very definite anemia which becomes more severe as the condition advances. They believe that pyelitis is either an etiological or aggravating factor in this anemia and that the anemia so lessens the resistance of the patient to infection that little improvement can be expected until it is overcome. For this reason they have added blood transfusion to the regular forms of treatment with a consequent 30% reduction in hospitalization, much lessened instance of ureteral catheterization and drainage, and an entire absence of necessity for therapeutic abortion.

Stallworthy was struck by the number of deaths occurring directly from obstetrical hemorrhage(over 300 per year in England and Wales) and by the small percentage of attempts made to restore blood in those cases in England(75). He reminds the reader that many of the most severe hemorrhages are preceded by a significant warning such as the preliminary small losses in placenta previa. In this case, he condemns those who wait for severe hemorrhage before typeing the patient and arranging for transfusion. He describes several technics and routines which have made immediate transfusion available to the physicians in his section and concludes with the plea that immediate transfusion technic be made ready for the extreme collapse caused by bleeding in ectopic pregnancy, hydatidiform mole, abortion, and severe antepartum or postpartum hemorrhage regardless of the cause.

Evans and Hart(76) have used and recommend transfusions as an adjunct to serum therapy in overcoming the toxemia and leukopenia of certain cases of pneumonia. They choose for these cases, patients who have a dropping white cell count, extension of the pneumonic

process progressively, and clinical signs of increasing severity after a period of six days. They cite the results of similar treatment at Duke Hospital where these cases had a period of 7.9 days between the onset and crisis as compared with 9.9 days in a control group.

One recent British paper(77) is interesting because the only cases cited for blood transfusion are those of hemorrhage. It seems the difficulty in that country is not with classifying the indications for blood transfusions but deciding on the finer aspects of giving blood in cases of hemorrhage.

A somewhat radical statement but one with some truth has been made by Johnson(78) when he says, "Transfusion of blood, which has held the center of the stage for so long, has, as we well know now, very great limitations, of which only recently the profession has become aware. When one has said that with the exception of recent hemorrhage and in certain hemolytic states its value is probably of little or no value, even in the face of much disagreement, we feel its status has been declared."

PART III

SUMMARY
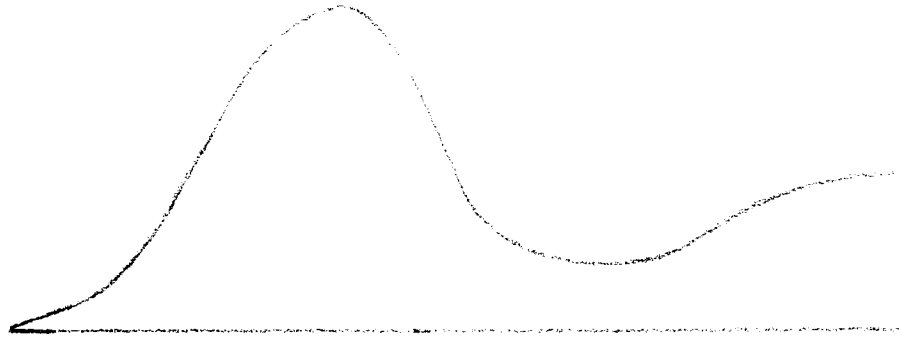
As regards the use of plasma and serum, I think it must be realized that they are relatively new therapeutic agents and have not yet been firmly established as regards their indications. The curve above may be called the popularity curve for nearly all new therapeutic agents. They are discovered, rapidly rise to a peak of use in too many conditions and then something happens to throw them into subtotal disrepute. Further work and familiarity gradually brings these substances back into use in progressively rationalized procedures.

It seems that plasma and serum are on the up-grade of this curve with their exact position being varied according to the geographical location of the workers using them. Thus, in England with its war and demand for agents that can be used in emergency when blood is not available, the position of these agents is higher up in the initial up-curve. In this country, their use is being preceded more by experimentation with the result that they are lower down on the curve.

Blood, on the other hand, has gone through these stages for the most part and established with minor fluctuations on the final level. Even the newer technic of preserving blood which has made possible the

blood banks has not changed its position greatly.

It must also be recognized that plasma and serum are used for their different properties. In some conditions, it is the hypertonic property made possible by the lyophile process that is desires; and in other conditions, it is the inherent qualities of the plasma itself that are desired.

It seems to me at this stage, the most logical procedure for choosing the indications for plasma and serum is to consider it in the light of its physical and biological makeup. When this is done, one is able to determine whether or not the qualities present will make it a suitable agent for use in a condition which requires certain substances or actions to combat deficiencies shown to be present in clinical and experimental procedures.

It seems that severe burn cases constitute one of the leading indications for plasma or serum. It is evident from reading the work abstracted, that these cases show a loss of serum proteins, hemoconcentration, and a secondary decrease in the osmotic tension of the blood stream. It may be further observed that crystalloid solutions have been found to be inefficient for several reasons including the inability of the human organism to supply sufficient protein from its reserves to make up the deficiency. Therefore, plasma, with its colloidal properties and its composition would seem to be the logical adjunct to established measures in the treatment of burn cases.

The case of shock is more difficult to rationalize. It is obvious that the shock due to hemorrhage is better treated by blood

transfusion than by plasma transfusion. In the cases where there is
no hemorrhage, the known pathology seems to consist mainly of packing
of the red cells in certain inaccessible compartments of the vascular
system, temporary capillary permeability to the plasma proteins, and
secondary anoxia due to decreased volume of the circulation. In the
face of evidence from the British that these so-called storage sites
for red cells can be made to release their captives by administra-
tion of plasma, it seems that plasma will replace blood to a large
extent in the treatment of this condition. At any rate, here is a
condition which gives one a chance to use nice judgement.

The use of plasma in hemorrhage must necessarily be reserved for
those cases in which the blood loss is not too severe to be repaired
by the stimulated hemopoietic system and for those cases in which
blood is not available, i.e. as an emergency treatment.

The cases of hypoproteinemia, if too severe or accompanying con-
ditions that will not permit replenishing by the organism, should
have the benefit of plasma transfusion. The special case of nephro-
sis will require more work; but at present, evidence seems to sug-
gest that there is set into motion some obscure, beneficial mech-
anism in about two thirds of the cases resulting in a crisis not
unlike that seen in the spontaneous crisis of this condition.

In cases of intestinal obstruction where there is a measure-
able decrease in the serum proteins, plasma seems to be indicated.

The concentrated plasma and serum apparently have their great-
est use thus far in decreasing the high intracranial pressure and in
nephrosis. This effect seems to be a direct consequence of the hyper-

tonicity and the property of prolongation of effect through the imper-meability of the capillaries to these substances. On the basis of the work so far done, it is not possible to make any final statements.

In the final analysis, a good criterion for the choice of plasma or serum or of blood could be developed by simultaneous determinations of the red cell count, hematocrit reading, plasma protein, and cir-culating blood volume. By comparison of these factors, the status of the condition could be recognized; and when tempered by clinical judgement and knowledge of the conditions, the choice should be more readily made.

In considering blood transfusion, I think it is commonly agreed that hemorrhage, regardless of the cause, is the first indication. That plasma will encroach upon blood in this respect seems highly improbable.

In shock associated with hemorrhage, blood should be the choice transfusate according to the best evidence presented. In shock with-out hemorrhage, I believe plasma will become the substance of choice in transfusions. I repeat that shock is a syndrome which allows or requires the judgement of the practitioner because of its varied appearance and because of the associated conditions which act as its cause.

I think there is no one who hesitates to give blood in the acute stage of idiopathic thrombocytopenic purpura unless it be because of fear of reactions. It is also obvious that the measure is a tem-porary one to tide the patient over until other measures can be taken.

In a similar way, blood seems to be indicated in hemophiliacs as a precautionary measure preceding surgical procedures rather than as a curative measure.

Vitamin K and bile salts are largely replacing blood transfusion in the jaundice cases. Blood, however, is still a valuable adjunct and is apparently being used by many men.

Blood is also indicated in certain types of poisoning in which the patients hemoglobin is tied up in such a way with the poison that it can not function as an oxygen-carrying substance. The usual example of this type poisoning is that which occurs with carbon monoxide. It is generally arranged to do a simultaneous venepuncture so that this really amounts to a replacement type of therapy.

I hesitate to make a definite stand on the question of bleeding peptic ulcer as an indication for transfusion. It seems, however, that the drip method of transfusion is making this measure more acceptable to many men. It seems there comes a time when the shock is so profound in these cases, that even the men most antagonistic to the procedure are willing to let their case be the exception that proves the rule.

Liver, in the case of macrocytic hyperchromic anemias and iron in the microcytic hypochromic anemias have made blood transfusion a less frequently used procedure in these cases. There are cases, according to the work presented, that need transfusion in this case either because these methods fail or because they have not time to allow them to wait for the effect.

Transfusion is used by many in the leukemias. The rational

is not concerned with the hope of cure but with the hope that the
diagnosis may turn out to have been missed.

The immuno-transfusion is not included in this paper, but it
seems there is much to be said for this procedure in the relatively
early stage of investigation.

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