THE CONTROL OF BLOOD TRANSFUSION HAZARDS*

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IN PRESENT DAY MAJOR SURGERY blood transfusion is perhaps next to anesthesia the most important adjunct contributing to the safety of the patient. At the present time it is not uncommon to have 4000 to 12,000 transfusions per year administered in the larger hospitals with active surgical services. The average rate in the general hospital is about six transfusions per bed per year.

Prior to Landsteiner’s discovery of the blood groups1, 2 in 1900 the chief danger of transfusions was intravascular hemolysis. So great was the resulting mortality that less than 400 transfusions were reported previous to this discovery.

With the classification of the blood groups by Jansky3 and Moss4 and the application of these discoveries to routine transfusions by Ottenberg and Libman5 the demand again became large, but the difficult technic of end-to-end anastomosis, Kimpton-Brown paraffined tubes and the multiple syringe method of Linderman6 prevented wide application. About this time a second risk was recognized when McClure7 transmitted syphilis from the donor to the patient in using the syringe method.

Beginning in 1914 the use of sodium citrate, popularized by Lewisohn,8 made possible the much simpler indirect transfusions, so simplifying the procedure that it was widely used in World War I.

In the early period a third and fourth risk were recognized in this stage of development, namely the reactions characterized by chills and fever and those of increasing severity and number occurring in patients receiving multiple transfusions, such as the cases of pernicious anemia, characterized by chills, fever, respiratory distress and shock. The third risk was explained by the discovery of "pyrogens" by Seibert9, 10 in 1923. The fourth risk is probably explained by discovery of the Rh factor through the work of Landsteiner and Wiener11, 12 and Levine and his associates.13

The fifth and the most serious transfusion risk next to that of intravascular hemolysis is that of homologous serum jaundice. First demonstrated by Beeson,14 and Morgan and Williams15 in 1943, jaundice has been recognized as a risk associated with the transfusions of pooled plasma, since there is an incidence of 4.5 to 7 per cent following its administration.

Following the original discovery of blood groups Landsteiner\textsuperscript{2} suggested that the presence or absence of isohemo-agglutinogens in the red cells determined these groups, and the groups were named for these agglutinogens.

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<tr>
<th>Group</th>
<th>Agglutinogens</th>
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<td>AB</td>
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<td>A</td>
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<td>O</td>
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The presence of six subgroups $A_1$, $A_2$, $A_1B$, $A_2B$, $A_3$ & $A_3B$ may be a serious interfering factor in blood grouping and in the use of group O as a universal donor. Usually careful grouping and the use of identical groups in transfusion cross-agglutination between donor and recipient will eliminate the possibility of dangerous incompatibilities which result in intravenous hemolysis.

An antiserum, produced when rabbits are injected with the R.B.C. of the Rhesus monkey, will agglutinate the R.B.C. of 83 per cent of the white race. Landsteiner and Wiener\textsuperscript{11} who, in 1940 demonstrated this new antigen, called it Rh factor, believing it to be a single entity inherited as a dominant trait. In the intervening nine years at least eight antigens of this type and hence as many Rh types have been discovered.

This discovery of the Rh factor and the classification of individuals as Rh positive and Rh negative explains to a large extent at least the hemolytic disease of the newborn and hemolytic reactions that follow repeated transfusions of bloods that are compatible as far as the A.B.O. system is concerned.

DeGowin\textsuperscript{16} with characteristic bluntness states, “It is doubtful whether any large series of blood transfusions has ever been given without hemolytic complications, some of which have been fatal. . . . Probably one to five hemolytic reactions per 1000 transfusions are inevitably caused by human error.”

Although the various possible factors have been given much consideration in the etiology of hemolytic reactions, particularly the red cell stroma and the freed potassium, it is the consensus of opinion at present that the released hemoglobin is the principal element of danger, since the entire syndrome can be produced with especially prepared and preserved crystalline oxyhemoglobin.

Low potassium values in the blood may be encountered following transfusions in various conditions where there has been marked potassium depletion in the tissues as in shock, infant diarrhea, etc.\textsuperscript{17}

Usually the first and often the most characteristic manifestations of intravascular hemolysis are chills, pain in the chest and legs, respiratory distress and shock. If the amount of hemolyzed blood is small (60 to 300 cc.), or the patient is under an anesthetic, only the fall in blood pressure may be noted.

If the first 100 cc. of blood are given slowly (15 minutes) to the unanesthetized patient under the close observation of the physician, the administra-
tion of lethal doses of incompatible blood should be avoided. Patients almost without exception survive the initial shock associated with hemolytic reactions, but the associated stagnant anoxia along with acidosis and dehydration contribute to more serious and fatal complications, that is, the so-called "lower nephron syndrome" or "renal anoxia." This syndrome is forecast frequently by hemoglobinuria, oliguria and anuria terminating with complete irreversible renal insufficiency in about half the cases.

The administration of blood to the anesthetized patient involves additional hazards more than justifying the use of plasma, albumen solutions and blood substitutes, with reconsideration and re-evaluation of the whole subject of operating room intravenous therapy.

Another source of intravenous hemolysis is isoimmunization, which results from having received incompatible blood of the A.B.O. or Rh systems through an earlier transfusion and in the case of the pregnant woman from carrying a fetus of different type. This source of hemolytic reaction is small at the present time due to the careful typing in both the A.B.O. and Rh systems with cross matching of all donors and recipients.

**CASE REPORTS**

**Case 1.**—G. H., Hosp. No. 500381, Path. No. 107262, Autopsy No. 5245, was a white male, age 43; admitted August 6, 1947. Died June 30, 1949. This 41-year-old bricklayer came to the emergency room of HFH complaining of pain in the right shoulder of 3 months' duration. Chest stereos were obtained which revealed an infiltrative process in both apices. Laboratory results showed the hemoglobin to be 13.2 Gm. and RBC 4.41 million. The WBC was 14,600 with 75 per cent polys. The sputum was positive for acid-fast bacilli.

The chest roentgenograms continued to show advanced pulmonary tuberculosis of both apices with cavitation. Twenty-two months after admission a left, first stage thoracoplasty was performed under ethylene and cyclopropane anesthesia. Five hundred cc. of type O blood were given during the operation and 500 cc. of type O blood on return to his room. Both transfusions were without reaction. He did not void in the first 24 hours. The NPN rose to 82 on the second postoperative day. The CO₂ was 39.6 volumes per 100, the serum chlorides 547, the sodium was 296. The urinary output on this day was 100 cc. and examination showed the specific gravity to be 1.016. The specimen contained

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4+ albumin and was mahogany-colored. The urinary output continued to be low, the NPN rose to 195, the potassium was 19.6 mg. per 100 and rose to 24.3. The patient died on the tenth postoperative day.

Autopsy showed some generalized edema. The lungs were edematous and increased in weight. The liver weighed 1700 Gm., and the usual architecture was well made out. The kidneys weighed, respectively: right 300, left 340 Gm. The cortices average 1.5 cm. in thickness, and were dark red in color. The pyramids, in contrast, were grayish-blue in appearance.

Microscopic examination showed the distal convoluted tubules having cells flattened and the lumina containing brownish granular debris or solid, brassy casts. The collecting tubules showed even more granular debris and brassy casts. There was some PMN infiltration throughout the interstitial tissue and some leukocytes within the lumina of the tubules.

The anatomical diagnosis was: postoperative state following recent thoracoplasty on the left; bilateral fibro-caseous tuberculosis; and lower nephron-nephrosis.

The almost universal use of blood stored in blood banks for periods up to 21 days adds other important possibilities of hemolytic reactions due to hemolysis of cells that takes place during storage. Factors that may be responsible are bacterial contamination, freezing and thawing, and absence of, or inadequate refrigeration. The addition of 50 per cent glucose, or a large amount of 5 per cent glucose at room temperature added to cold blood, such as happens when the intravenous is started with glucose and the blood backs up into the glucose throughout a long operative procedure, may also result in extensive hemolysis, according to De Gowin.18

PYROGENIC REACTIONS

The non-specific reactions characterized by chills and fever of varying degree were observed much more frequently associated with the indirect or citrate method of transfusion. In fact, the citrate itself and the so-called precoagulative changes in blood transferred by this method were blamed for these annoying, though rarely serious reactions until Seibert9, 10 in 1923 showed they were due to certain nonpathogenic bacteria producing thermosable protein substances in the water, now designated as pyrogens.

The great difficulty of freeing contaminated water of these pyrogens in the average hospital solution room has resulted in a new and profitable business, that of manufacturing and distributing pyrogen-free intravenous solutions, which materially increases the cost of medical care.

TRANSFUSION TRANSMISSION OF DISEASE

The transmission of syphilis by transfusion was reported soon after the discovery of the A.B.O. blood types and its resulting re-establishment as a safe therapeutic procedure. Fordyce18 referred to the case of Dade in 1915 and McClure7 published his own case report in 1916.

In the 25 years following these first reports over 100 cases of syphilis resulting from transfusion either were reported privately or were published.
This was in the period during which the serologic tests for syphilis were being improved and standardized and before blood banking came into general acceptance and use. Eichenlaub and Stolar\textsuperscript{10} state that in 18 out of 41 cases, or 44 per cent of transfusion syphilis, serologic tests would have been of no assistance. Apparently the greatest hazard is with the donor in the preclinical serologically negative stage as McClure's case was.

The present use of supersensitive screen tests for syphilis, such as the Kahn presumptive and the Kline exclusion, will pick up the infection earlier. The storage at 4° C in the refrigerator for a period of three days will kill the treponema pallidum if present. The use of both these precautions should eliminate transfusion syphilis. When friends and relatives are used, it is occasionally difficult to find a donor with a negative serologic test for syphilis. In one case each of seven donors had to be refused on this basis. Hoxworth and Skinner\textsuperscript{20, 21} found 7.5 per cent of blood drawn from 3487 donors showed positive precipitation tests and it was discarded on that basis. If 7.5 per cent of the 13,500,000 units of blood collected by the American Red Cross during World War II had been discarded, more than a million units would have been wasted. At the present time serologically positive blood should be sterilized or refrigerated and the plasma used for fractionation.

The transmission of malaria by transfusion is, of course, less serious than the transmission of syphilis. The first case was reported in 1920 by Woolsey;\textsuperscript{22} and since that time some 85 cases have been published. Wang and Lee\textsuperscript{23} in 3700 transfusions in China found benign Tertian malaria in 14 per cent of their patients. Although benign Tertian malaria is the usual type transmitted, McClure and Lam\textsuperscript{24} reported two cases of quartan where the donors were Italians with no symptoms of or exposure to malaria for many years.

Here neither storage in the refrigerator at low temperatures nor examination of blood smears is of material assistance. Exclusion of donors who have had malaria or are from known malaria countries or regions, is apparently the only method of prevention unless some method of actual sterilization is found.

The most serious of all the diseases transmitted by transfusions of blood and plasma is homologous serum jaundice, which was first recognized as a separate entity in 1937. Oliphant\textsuperscript{25} reported jaundice following the administration of human serum in 1943. Neefe, Stokes, Reinhold and Lukens\textsuperscript{26} in 1944 studied hepatitis due to the injection of homologous blood products in human volunteers, and Paul, Havens, Sabin and Phillip\textsuperscript{27} did transmission experiments in serum jaundice and infectious hepatitis in 1945. Grossman, Stewart and Stokes\textsuperscript{28} reported post-transfusion hepatitis in battle casualties and its prophylaxis by means of human immune globulin late in 1945. Brightman and Korns\textsuperscript{29} found an incidence of 4.5 per cent of homologous serum jaundice from pooled plasma in this country in 1947, a year after Spurling.
Shone and Vaughan\textsuperscript{30} reported an incidence of 7.3 per cent among 1054 patients receiving pooled plasma in England.

McGraw, Strumia, and Burns,\textsuperscript{31} published in 1949 the results of a four-year survey to determine the incidence of post-transfusion hepatitis as it occurred at the Bryn Mawr Hospital. Of 936 transfused patients there were 32 or 3.5 per cent with probable or possible hepatitis. These patients received 3723 transfusions, hence there was one case of probable hepatitis for every 300 units of blood transfused. Of 528 patients receiving plasma from small pools of eight or ten units with or without whole blood, ten had probable hepatitis, an incidence of one in every 235 plasma transfusions. As pointed out by these authors, the lower incidence of hepatitis in this group is probably due to the small pools of plasma, eight to ten units, as contrasted with pools of 25 to 50 in the American Red Cross material and up to 800 in the British pools.

In the Henry Ford Hospital Steele\textsuperscript{32} has studied 26 cases of homologous serum jaundice and 63 cases of infectious hepatitis occurring over a two-year period. Of the 63 cases of infectious hepatitis three died, giving a mortality of 4.8 per cent. Of the 26 cases of homologous serum jaundice nine died giving a mortality of 34 per cent. The mortality of 34 per cent as compared with 4.8 per cent for infectious hepatitis is unusually high. Eighteen of the latter group received their transfusions in the hospital. Three received plasma only, 11 received whole blood alone and four received both blood and plasma. Since approximately 8000 transfusions were administered within the hospital in these two years, there was one case of jaundice for every 440 transfusions.

**Case 2.**—H. T., Hosp. No. 385096, was a white female, age 18, and married. She was re-admitted to the hospital June 14, 1948, and died June 18, 1948. The patient was a primipara with an uneventful prenatal course. P. E. was negative throughout, essentially. Her Hb. on October 4, 1947, was 11.5 Gm., Rh factor was positive, and blood group O. The delivery was by outlet forceps on April 5, 1948. Left mesiolateral episiotomy was done. Upon delivery of the placenta the patient bled profusely in spite of intravenous pitocin and ergotrate and massage of the uterus. The patient was given 1000 cc. of plasma and this was followed by 1300 cc. of blood group O, Rh positive, donors. Following this the patient's blood pressure improved, and she was returned to her room in fair condition. The patient was discharged from HFH on the seventh postpartum day. T. 99, pulse 108. The Hb. was 12.0 Gm. The patient was seen in the Clinic on May 11. At that time the uterus was forward, undergoing normal involution. Intervening examinations were uneventful. On June 11 she complained of generalized malaise and some pain in her chest. Her lungs were clear. She was urged to have some rest. On June 14, 1948 she was admitted on G. I. service. She had been jaundiced for 3 preceding days, and had had persistent nausea since her delivery and vomiting for the preceding week. Temperature was 101.8\textdegree, BP 130/68, and there was a definite icteric tint of the skin and sclerae. The liver was palpable and tender 7 cm. below RCM; otherwise negative. Hb. 12, RBC 4.36, WBC 7150, with 62 per cent PMN, 38 per cent L. Routine urine analysis was negative. Quant. urine urobilinogen .38 units per 100 cc. The prothrombin time was 25"—27 per cent, and
cephalin cholesterol was 4+. The thymol turbidity was 3 units, the Icterus index 82, and the basic phosphatase 7.37.

The patient was given I. V. protein-hydrolysate solution, choline chlorides, vitamin B complex, high protein, high carbohydrate diet. She developed a febrile reaction to protein-hydrolysate and went into a delirium, became semicomatose and developed generalized convulsions. Blood sugar on June 18 was 26 mg per 100 cc. She died that evening, following a convulsion.

Autopsy showed generalized icterus with 200 cc. yellowish-green fluid in each pleural cavity, 1000 cc. of greenish abdominal fluid, and numerous petechiae over serosal surfaces. The liver was soft, semifluid in consistency, and weighed 950 Gm. The kidneys weighed 200 Gm. each, showing considerable bile staining.

The microscopic pathology showed almost complete necrosis of liver cells, leaving only lobular framework, with fine, granular, pink-staining debris scattered throughout.

The anatomical diagnosis was acute necrotic hepatitis (homologous serum jaundice).

CONTROL OF HOMOLOGOUS SERUM JAUNDICE

Since the etiologic agent of homologous serum jaundice has not been isolated and no susceptible animal has been found, the laboratory is of little aid in the diagnosis. This necessitates control measures of the less direct and less adequate type. Careful selection of donors and limitation of plasma pools to one to ten units appears in McGraw, Strumia and Burns' work31 to be helpful. Stokes, Blanchard, Neefe, Gellis and Wade33 found that two injections of gamma globulin made from large liver cell pools of human plasma given during the incubation period were highly protective in one hospital, while in two other hospitals it was of little value.

Oliphant25 in his Harvey lecture 1944 stated: "Since jaundice has repeatedly followed the administration of whole blood and blood products, there is an urgent need for some means of detecting the presence of the jaundice producing agent in the blood and for some practical method for treating blood products, so that the danger of jaundice following their use may be eliminated." At the same time he reported that irradiation of pooled serum in a Quartz cell with a mercury vapor lamp for 2½ seconds inactivated the icterogenic agent. Oliphant and Hollaender34 followed this with a report of the use of irradiated serum in human volunteers in which four out of 12
receiving the control material and one of 12 receiving serum irradiated for six minutes developed jaundice.

This work was followed by numerous applications of the irradiation principle with various types of equipment. MacCallum in England was unable to confirm Oliphant's work, but more recently Habel and Sockrider, Wolf, Mason, Fitzpatrick, Swartz, and Levinson, and Blanchard, Stokes, Hampil, Wade, and Spizizen have confirmed and extended the method and application. The latter group, after trial on human volunteers, find irradiation safe and effective. The treated plasma showed no alteration in the electrophoretic pattern, and they recommend its routine use.

Hartman and Mangun recently demonstrated the feasibility of chemically inactivating viruses in both plasma and whole blood, using methyl-bis (beta-chloroethyl) amine (HN2) and related alkylating compounds. It was shown that these compounds exerted a satisfactory inactivation of five neurotrophic viruses, viz., New Jersey vesicular stomatitis, lymphocytic choriomeningitis, St. Louis encephalitis and Eastern and Western equine encephalitis, in the presence of whole blood and blood plasma. These findings are supported by the observations of Tenbroek and Herriott, and Rose and Gellhorn on the virucidal action of HN2 on five other viruses in the absence of blood.

The method is simple and easily applied. The HN2 or related compound is dissolved in distilled water and added directly to the blood or plasma. The treated material must have a pH above 7.3 to permit rapid degradation of the excess HN2 and below 7.8 to obtain maximum virucidal activity. The treated material is then stored at 4 to 10°C for not less than five days, then a small amount of sodium thiosulfate is added to decompose any remaining traces of HN2. Before use a sensitive color test is applied to further insure that no active toxic agent remains.

**EFFECT OF HN ON PLASMA**

HN2 is not without certain disadvantages. It partially inactivates components of the clotting system, including prothrombin and accelerator globulin. The amount of fibrin formed is not altered, but the rate at which it forms is appreciably slowed even when preformed thrombin is employed as the clotting agent.

Complement, syphilis antibodies (Kolmer Wassermann), and B. abortus antibodies (complement fixation) are only very slightly reduced by sterilizing dosages of HN2.

No significant changes occur in the albumin/globulin ratio nor in the electrophoretic pattern of treated plasma.

The thermal stability of albumin is not significantly altered, according to Mulford, although the reaction of HN2 with albumin has been demonstrated to occur (Mangun).

In the course of the reaction of HN2 with plasma, the formation of toxic intermediary addition products with proteins has been shown to take place.
These further degrade to nontoxic end products, but suitable conditions of pH must exist to ensure their disappearance.

**EFFECTS OF HN₂ ON RED BLOOD CELLS**

At dosages of HN₂ required to sterilize whole blood (500 mg./l), there is a remarkable absence of effects upon the red blood cells. It has been shown by our laboratory that even at dosages of HN₂ several times that required to sterilize whole blood, the red blood cells behave in all respects *in vitro* similar to the control specimens. There is virtually no increase in fragility to hypotonic solution. The rate of loss of potassium from the red cell is similar to that of the controls. On long standing, the degree of hemolysis of the treated blood is, if anything, slightly less than in the untreated controls. Sedimentation rate remains essentially normal. Glycolysis, as measured by the disappearance of glucose, is unaffected. Conversion of hemoglobin to methemoglobin on long standing proceeds at about the same rate in treated and untreated blood. The hemoglobin absorption spectrum is unaltered. No studies have been made on the oxygen dissociation constants, nor on the activity of carbonic anhydrase.

The *in vivo* survival of the red blood cells has been investigated both in this laboratory and by F. H. Bethell at Ann Arbor. Both of these investigations have led to a similar conclusion—the *in vivo* survival of the red blood cells is equal to that of the control bloods, if not slightly superior.

**GENERAL**

The principal disadvantage to the use of HN₂ in the sterilization of plasma and whole blood lies in its toxicity. Although it hydrolyzes over a period of hours or days, depending upon temperature and pH, the toxicity of the original compound and some of its intermediaries and intermediate protein addition products requires that careful control be exercised over the process. The greatest single danger lies in the stabilization of the protein addition product by pH values below 7.2. It is, therefore, necessary in the sterilization of whole blood to collect the blood in a modified ACD solution to which alkali has been added, so that the pH of the blood after the addition of HN₂ will never be lower than this value. Adequate precautions must then be taken to insure that the blood is not released until the aging period has expired.

Hartman and Mangun have been conducting further studies on new virucidal agents. At least three separate families of compounds have now been discovered which possess a high order of virucidal activity *in vitro* in the presence of plasma or whole blood. While HN₂ at the present time is superior to other agents for the treatment of whole blood, there appears to be little doubt that these investigations will eventually disclose other compounds equal or superior to HN₂ in their virucidal activity, yet eliminate the dis-
advantages of this particular substance. In the meantime, in view of the urgency of this problem, clinical application of HN2 on a substantial scale to the sterilization of plasma is being carried out. In a total of approximately 975 plasma transfusions given over a period of ten months to approximately 400 patients, not a single case of hepatitis has been observed in contrast to a predicted 20 cases in untreated plasma.

No evidence of unfavorable reaction nor hematologic changes has occurred in adults or older children. In the course of these studies leukopenia occurred in very young children prior to the recognition of the intermediate protein-HN2 reaction-product previously mentioned. Since this hazard has been recognized, a color test has been developed to detect this substance and the sterilization procedure modified to eliminate possible danger.

SUMMARY AND CONCLUSIONS

1. The present-day large scale use of blood transfusions keeping pace with the constantly increasing range and extent of surgical procedures is a protection. It involves a correspondingly increased risk, particularly in the way of hemolytic reactions with possible kidney insufficiency and homologous serum jaundice with liver necrosis and insufficiency.

2. To avoid hemolytic reactions greatest care must be exercised in the medical supervision and operation of the blood bank and the whole transfusion procedure. Probably the smoothest and safest operation is obtained by a transfusion team which is responsible for every phase from the original bleeding of the donor, sterilization, grouping, cross agglutination, storage of the blood and the final administration to the patient.

3. To eliminate homologous serum jaundice, nothing short of sterilization of both plasma and whole blood seems acceptable.

BIBLIOGRAPHY


CONTROL OF BLOOD TRANSFUSION HAZARDS


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DISCUSSION.—DR. EVERETT I. EVANS, Richmond, Va.: I think some of us who are not too well acquainted with the theoretical and practical import of this paper may not recognize its true significance. One reason is that, as surgeons, we tend more and more to delegate the care of patients to people who are not directly responsible for the fatality that may ensue. In my experience and the experience of Doctor Bigger in our hospital, and I think in the experience of most people who are interested in the matter of replacing material lost from the blood stream through trauma or surgical operation, it becomes evident at once that what is needed in replacement therapy is not plasma, but whole blood. I have said that so often that I am beginning to be ashamed of saying it again; but it must be understood. We need blood, not plasma. If that is understood there need not be much plasma made, and if that dictum is followed there will not be anywhere near the danger of transmission of serum hepatitis. The great hazard of transmission of hepatitis virus by plasma as contrasted with whole blood results from the pooling of plasma. This greater hazard is a simple mathematical matter. So I say again that we should impose on ourselves the idea that we need whole blood, not plasma, and thus we will greatly lessen the incidence of serum hepatitis.

I believe more work should be done on preparation and trial of so-called plasma substitutes, until we have methods that will truly sterilize plasma; to date this has not been done. We are extremely interested in the work Doctor McClure’s group is doing with Doctor Hartman in the use of nitrogen mustard, but a vastly greater trial of this material must be carried out before we can be sure it is safe.

Finally, I will only say again that in the problem of replacement therapy, whole blood is the agent that is needed, and not plasma.

DR. ALLEN O. WHIPPLE, New York: Doctor McClure asked me to say a few words about the use of transfusion, possibly because they have more transfusions at Memorial Hospital than in any other hospital in the city of New York. There is no question that transfusion is one of the greatest aids to the surgeon, and yet the amount of blood to be