CARDIOVASCULAR AND CLOTTING DISTURBANCES DURING MASSIVE BLOOD REPLACEMENT

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The relatively recent approaches of surgery to the treatment of cancer and cardiovascular abnormalities have resulted in the administration of bank blood at rates and in amounts far in excess of those previously studied and demonstrated to be safe. In many instances massive blood replacement may amount to practically complete replacement of the patient’s blood with blood obtained from donors and preserved for varying periods under the nonphysiological circumstances occurring in standard blood bank practice.

While most patients seem to receive such transfusions without apparent untoward effect and while it is often difficult to ascribe any untoward effect that may occur to the transfusions alone, to the exclusion of all the other factors involved, such as, the operative procedure, the amount and degree of shock, or the anesthesia, it is nevertheless apparent that there is a high incidence of thus far unexplained abnormal reactions among patients who are massively transfused. In a series of cases of patients receiving multiple transfusions mortality increased markedly above 15 units of blood, and survival after 20 units was not common (1).

Among the reactions of grave significance which have been reported with massive blood replacement are: first, persistent vascular oozing from the operative and other sites (1); second, the occurrence of cardiac arrhythmias, ventricular fibrillation (2), or cardiac arrest; and third, the development of “citrate intoxication” (3).

Before a discussion of the complications of massive blood replacement is begun, a consideration of the contents of a bottle of citrated bank blood is necessary. This is important since the administration of one blood volume as replacement therapy to a patient will result in 62 per cent of donor blood in the patient’s circulation, and the administration of two blood volumes (approximately 20 pints) leaves the patient with only 13 per cent of his original blood volume (4).

A unit of citrated bank blood contains 120 cc. of acid citrate dextrose (ACD) solution (solution B of the National Institute of Health) and approximately 480 cc. of donor blood. Solution B contains trisodium citrate, 13.2 Gm., citric acid, 4.9 Gm., and dextrose, 14.7 Gm., diluted to 1,000 ml. with distilled water. The physical characteristics of bank blood when administered are a temperature between 4 C. and 10 C. (2),

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a hematocrit determination between 40 and 60 per cent (5) and a pH of approximately 6.6 to 7.1 (6), a shift of the oxygen dissociation curve to the left (6), an increase in free hemoglobin (7) and potassium (8) and a depleted unbound calcium in the plasma (9). There is, additionally, a deficiency of platelets, antihemophilic globulin, and the labile factor, all elements which are necessary for blood clotting (17).

**Blood Clotting Disturbances**

An understanding of the development of the hemorrhagic diathesis occurring during massive blood replacement requires a working knowledge of the hemostatic processes occurring *in vivo* (10). Trauma to small vessels is followed within 15 to 30 seconds by a localized vasoconstriction. Next, an agglutination of platelets occurs in any area where the continuity of the vascular wall has been erupted. This agglutination and subsequent lysis of the platelets is followed by the liberation of serotonin (5-hydroxytryptamine). Serotonin is a powerful vasoconstrictor for vessels both intact and injured, local and distant. This vasoconstriction may occur for as long as 30 minutes. Following the vasoconstriction the fibrin clot is formed within a few minutes. The fibrin clot then begins to retract and by approaching the wall of the vessel assures better hemostasis.

An important factor in the above mechanism is the function of the platelets (10). This is especially important in the syndrome we are considering, namely, the administration of large amounts of stored bank blood which is practically platelet free. The function of the platelets are many and varied. The platelets liberate a vasoconstrictor principle (serotonin); participate in clot retraction; contain agents which participate in the activation of thromboplastin (PTF, platelet thromboplastic factor); and accelerate the conversion of fibrinogen to fibrin (platelet factor 2).

In addition to the platelets, a number of plasma proteins are involved in the process of blood coagulation (11). These are: (1) agents taking part in the formation of thromboplastin (antihemophilic globulin, plasma thromboplastin component, plasma thromboplastin antecedent, and others; (2) agents more directly involved in the formation of thrombin after thromboplastin has been evolved, (prothrombin, labile and stable factors); and (3) fibrinogen. There are also agents in the blood inhibiting the formation of the clot. The most important in massive blood replacement is the fibrinolytic system and this will be discussed later.

In the not too distant past the clotting of blood was simple to understand and explain. The classic theory of blood clotting consisted of two stages. These were the conversion of prothrombin to thrombin with calcium and thromboplastin acting as catalysts, followed by the conversion of fibrinogen to fibrin by thrombin. In the last few years
this simple hypothesis has been amplified into a jumble of dissimilar and complicated names often for the same factor. All authorities do not agree on the exact mechanisms of the coagulation process (11).

Authorities in the blood clotting field have postulated many complicated schemes of blood coagulation. An acceptable hypothesis is that of Stefanini and Damashek (12). For an extensive discussion of clotting disorders the reader is referred to their book.

For practical purposes blood coagulation may be divided into three phases. These are the formation of thromboplastin, the formation of thrombin, and the formation of fibrin.

The formation of thromboplastin results from the interaction between the platelets and several plasma factors. These plasma factors are antihemophilic globulin (AHG), plasma thromboplastin component (PTC) and the plasma thromboplastin antecedent (PTA). The detection of platelet abnormalities which may result in clotting deficiencies can be determined by a platelet count (which should be above 150,000/eu. mm.), a decrease in the clot retraction, and a bleeding time over 7 minutes. The detection of the plasma factor deficiencies depends upon a clotting time over 13 minutes, a prothrombin consumption under 90 per cent, an antihemophilic factor less than 30 per cent, and a plasma thromboplastin component less than 25 per cent.

The formation of thrombin depends upon an interaction between thromboplastin, calcium, prothrombin, the stable factor (proconvertin) and the labile factor (proaccelerin). The detection of defective thrombin formation depends upon the demonstration of a prolonged clotting time (over 13 minutes) and values below 65 per cent prothrombin, the labile factor and the stable factor.

The final phase of clot development is fibrin formation. This results from the interaction of thrombin and fibrinogen. Deficiencies of defective fibrin formation may be detected by the in vitro formation of a floc clot or the total absence of clot formation.

The remaining system of interest in the massive transfusion problem is the fibrinolytic system (13). This is an anticoagulant system, enzymatic in nature. This enzyme is profibrinolysin, which may be acted upon by tissue kinases (lung, uterus, pancreas), bacteria or epi-
nephrine. An antifibrinolysin and antifibrinolysokinase occur in the plasma which are capable of inactivating fibrinolysin. Ungar (14) has postulated the liberation of two factors from the spleen (in the guinea pig) which accelerate (splenic A) or decelerate (splenic B) the inactivation of fibrinolysin by antifibrinolysin.

The defects in the clotting mechanism which have been reported after massive blood replacement have been thought to be due to a deficiency of platelets, decreased ionized calcium, elevated plasma citric acid levels, fibrinolysis, decreased labile factor, hypothermia and incompatible transfusion reactions.

Thrombocytopenia following massive blood replacement has been
reported by Krevans and Jackson (15), Stefanini and co-workers (16), and Bell (17). However, in the Memorial Hospital series of 77 patients, although there was often a serious depression in the platelet levels, in only two patients was there less than 100,000 platelets per cubic millimeter and neither of these patients bled (18).

The decreased ionized calcium levels and increased citric acid levels which have been thought to cause bleeding after massive blood replacements, have not been incriminated in our series (19). These two phenomena will be discussed in detail in the section on "citrate intoxication."

Fibrinolysis or increased fibrinolytic activity of the blood after massive blood replacement has been reported by many authors and in many clinical situations. The most common cases in which fibrinolysis occurs are gynecologic surgery (10), pancreatic surgery (20) and thoracic surgery (21). As mentioned previously, the lung and uterus are known to contain kinase for profibrinolysin and the pancreas is an active source of proteolytic enzymes. In MacFarlane's series (22) 75 per cent of his cases showed fibrinolysis after operation, but in no cases were there any bleeding complications. Similarly, fibrinolysis has been shown to occur after massive transfusions by Stefanini (16), Coon (23), and others.

A decreased labile factor or Factor V has been incriminated as the cause of bleeding after massive blood replacement by Bell (17), Scott and Crosby (24) and by Zucker et al. (25) after hepatic surgery.

Hypothermia can result from the administration of large amounts of citrated cold bank blood. Coagulation changes during hypothermia have been reported by Ellis, Kleinasser and Speer (26), who found a depletion of labile factor, stable factor, prothrombin and fibrinogen in dogs undergoing hypothermia and cardiac surgery. Couves and his co-workers (27) found prolonged bleeding times and reduced platelet counts at lower temperatures. They felt that the increase in bleeding time might be due to altered capillary response to trauma as a result of cold, increase in venous pressure, or reduced platelet count. Deterling et al. (28) showed that there was an increase in the clotting time of hypothermic dogs. Bleeding has been found to be a significant problem in hypothermia during surgery by other authors (29, 30).

Frieson, Harsha and McCroskey (31) have postulated that abnormal bleeding is due to administration of incompatible blood. They believe this is a hemolytic reaction which responds to adequate toluidine blue therapy. This reaction may occur in humans after one or two transfusions and in dogs after many transfusions. In the series at Memorial Hospital, in no cases in which generalized oozing occurred was an incompatible blood transfusion demonstrated. This is believed to be due to the routine use of the Coombs test in the cross-matching of blood in the Memorial Hospital blood bank. Although the possibility of incompatibility still exists, it is our opinion that bleeding from wounds
during blood transfusion is usually due to some defect in the congluti-
tion mechanism and not to an incompatible blood transfusion.

Although temporary and moderate episodes of oozing occur from
small blood vessels during surgery, only a few cases are serious and
persist after closure of the abdominal wound. In addition, it has been
shown that in the presence of one defect in the clotting mechanism
oozing from the wound seldom occurs. There is, however, a statisti-
cally significant relationship between the occurrence of excessive bleed-
ing and the presence of multiple changes in the clotting factors studied
(18). The treatment of defects in the conglutination mechanism is seldom
necessary. The majority of cases of vascular oozing will cease at the
end of operation, and in only one case has a patient died from a defect
in the clotting mechanism which persisted after the termination of
surgery. Usually blood clotting factors return to normal within two
to four hours, and in the absence of an open vessel the patient is able
to finally clot his own blood.

Generally, in this hospital, the therapy for vascular oozing has
been aimed at correcting the demonstrated defect in the clotting
mechanism. Platelet deficiencies are treated either with fresh blood
drawn into plastic containers or silicone treated bottles. Defects of
accelerator globulin or labile factor can be treated with either fresh
bank blood or lyophilized plasma (antihemophilic plasma). A deficit
of fibrinogen can be treated with either whole blood which contains as
much as 250 mg. per cent of fibrinogen or with fibrinogen per se. When
fibrinolysis persists after closure of the wound antihemophilic plasma
has been used in several cases with excellent results. It must be em-
phasized at this time that the most effective treatment of vascular
oozing from a surgical wound is the cessation of the operative trauma
and anesthesia. It is the unusual cases that continue to ooze post-
operatively and in whom clotting studies may be of value.

Cardiovascular Changes

The cardiovascular changes associated with massive blood replace-
ment of citrated blood have been reported by Watkins (32), Cookson,
Costas-Durieux, and Bailey (33) and Senning (34) in dogs, and
Hubbard, Nies, and Barmore (35) and Howland et al. (1) in humans.
Watkins showed in dogs made hypotensive and treated with citrated
blood, that there is an enhanced toxicity of citrate accompanied by a
progressive elevation and peaking of T-wave patterns over the right
precordial vector electrocardiographic leads. He found T-wave peak-
ing to be eliminated by the injection of calcium. Cookson et al. (33)
found that dogs given citrated blood had a heart which became pro-
gressively weaker and went into arrest in diastole. He believed this
to be due to the fact that citrate effectively removes ionized calcium
from the blood and tissues and that the heart cannot beat in the ab-
sence of free calcium ion. Senning working with dogs again demonstrated the fact that hemorrhagic shock responds far more rapidly and with better results to heparinized blood than to blood made anticoagulant by ACD solution. He further showed that the citrate effect disappears if 10 ml. of 10 per cent calcium gluconate is used for every unit of blood. Hubbard reported on one case of a patient with tetralogy of Fallot who developed prolongation of the QT interval after injection of only 750 cc. of blood. This prolongation of the QT interval with an elevation of the T wave was reversed by the administration of 10 per cent calcium gluconate. This does not necessarily mean that the 750 cc. of blood produced the changes observed since these changes are often seen during cardiac surgery. Howland and his co-workers have shown in previous reports that there are two types of cardiac complications that occur with massive blood replacement. The first of these is ventricular fibrillation and the second is cardiac asystole. Premontory signs in both conditions have been shown to be prolongation of the QT interval, elevation of the T wave, distortion of the QRS complex and bradycardia. In a study of 253 cases of patients receiving massive blood replacement, there were 22 cases of sudden cessation of cardiac function which occurred in spite of adequate replacement of blood lost during the operative procedure. In 9 of these 22 cases, changes were demonstrated in the electrocardiogram diagnostic of ventricular fibrillation (2).

The factors which are responsible for the adverse cardiovascular effects with rapid massive blood replacement are not clear at the present time. There are several factors acting during rapid blood replacement both in the patient and in the blood administered which can result in these conditions. DiPalma and Schults (36) in 1950 listed a series of factors which they felt were significant in precipitating the appearance of ventricular fibrillation in nontransfused dogs. Included in this category were the rapid injection of potassium, a serum concentration of calcium higher than 30 mg. per cent and an increase in the hydrogen ion concentration of the blood with resultant hyperacidity. Several workers have shown the high incidence of ventricular fibrillation during induced hypothermia. All of these factors are available to act in patients receiving massive rapid blood replacement. Mencer (39) believes that an electrocardiogram showing peaking and elevation of the T waves, prolonged QT interval, and widening and disfigurement of the QRS complex is typical of potassium intoxication and hypocalcaemia. This pattern has been demonstrated in patients clinically during operative procedures. An elevation of the plasma potassium in the patient can easily result from the plasma of citrated bank blood. Crosby (40) has shown that the levels of potassium in bank blood plasma may approach 25 mEq. of potassium in three weeks. The problem of calcium depletion is at the present time unproved and will be discussed further in the section on “citrate intoxication.”
The pH of freshly drawn bank blood is 7.1 decreasing at the end of three weeks to a pH of 6.6. A change in pH in the direction of acidity, either locally or systemically has been shown to predispose to ventricular fibrillation (36). Acidosis increases and alkalois decreases the serum potassium concentration. For each 0.1 unit change in extracellular pH there is an inverse change of approximately 0.4 to 1.2 mEq. in the serum potassium concentration (37). The marked acidity of bank blood can result after several transfusions in an increase of serum potassium levels to as much as 3 mEq. per liter (38).

Ihypothermia, below 25 C., has been demonstrated to cause ventricular fibrillation in as many as one third of dogs (28). In patients in this hospital receiving 10 to 15 pints of blood within a period of three to four hours the temperature has been recorded rectally as low as 90 F. Kaminer and Bernstein (41) have shown that the application of cold to the anterior chest wall of man will result in depression and inversion of the T wave in leads V₁ to V₄ and a concomitant decrease in the plasma potassium concentration. They postulate that cold inhibits a chemical system in the myocardium concerned with the ionic exchange related to the repolarization process. Disturbance of this system may trigger a reaction effecting the potassium transfer from the extracellular to intracellular compartment. At the present time the influence of potassium on the heart is a complicated one, and depends among other factors upon myocardial anoxia and upon its direct action on heart muscle. In connection with myocardial anoxia the work of Valtis and Kennedy (6) assumes added importance. They found that in blood stored in an acid citrate dextrose medium at 4 C., the oxygen dissociation curve was shifted to the left, and the amount of carbon dioxide released for each volume per cent of hemoglobin saturation with oxygen was reduced. (For each volume per cent of oxygen saturation, hemoglobin normally releases 0.35 to 0.4 volume of carbon dioxide at plasma pH 7.4 and 0.3 volume at plasma pH 7.3. In stored citrated blood with plasma pH of 7.3 this volume is 0.2). These changes are progressive with storage. Oxygen dissociation curves of patients after transfusion with citrated blood stored 7 days or more were substantially shifted to the left immediately after transfusion and this effect lasted several hours. The magnitude and duration of the shift was proportional to the volume and length of time of storage of the transfused blood. As a result of this shift, the recipient's blood may be unable, for a few hours after transfusion, to release as much oxygen as it did before.

Thus, factors such as: an increased potassium, decreased body temperature, decreased pH and a shift of the oxygen dissociation curve; all factors that may contribute to the production of cardiac arrhythmia are present. Therefore, it is reasonable to suspect more than one factor is acting during the massive transfusion of blood to cause the cardiac difficulties which occur.
Citrate Intoxication

Citrate intoxication has been the subject of much clinical and laboratory investigation since the advent of the modern blood bank. Originally, it was thought that blood would not be administered at more than 2 pints per hour and in view of this fact, there was little danger of citrate intoxication. The effects of citrate intoxication which have been reported in the literature have been believed to have been due to decreased ionized calcium resulting in cardiac arrest, ventricular fibrillation, hypotension of a severe degree and clotting disturbances (2, 3, 33, 42-48). Therefore, a discussion of citrate intoxication should consist of two factors, elevated plasma citric acid levels in the body and its effect on ionized calcium and the homeostatic mechanisms in the body responsible for the maintenance of ionized calcium.

Citric acid occurs endogenously as a part of Kreb's cycle. The greatest quantity of citric acid is metabolized by muscle, the main site of carbohydrate metabolism, through the stages of cisaconitic and isoconitic acid in the presence of the enzyme aconitase. Citric acid occurs in the plasma at levels between 1 and 2.5 mg. per cent. The liver metabolizes citric acid, but Martensson (49) has shown that the liver is not essential for the metabolism of citric acid in the body. Bunker et al. (3) reported elevated citric acid levels during blood replacement in patients suffering predominantly from cirrhosis. Howland and his co-workers (19) showed that in patients with abnormal liver function tests, mainly owing to metastatic carcinoma to the liver, there was no elevation of plasma citric acid levels compared to those observed in normals. It may be that the metabolic disturbances associated with cirrhosis impair citric acid metabolism and account for this discrepancy. Additional support is given to this theory by a series of patients receiving citrated blood during hepatic lobectomy at Memorial Hospital (25). The rate of metabolism or clearance of citric acid in these patients was the same as that in patients undergoing nonhepatic operations and receiving equivalent amounts of blood.

The main source of exogenous citrate in the operating room is the acid citrate dextrose solution which is used as the anticoagulant in the bank blood. In the majority of blood banks in this country solution B of the National Institute of Health is used. One hundred twenty cubic centimeters of this solution is added to each bottle of bank blood to prevent coagulation, an equivalent of 1.43 Gm. of citric acid.

An understanding of calcium metabolism is necessary to evaluate the effects of massive blood replacement on the ionized calcium in the human body. The greatest amount (99 per cent) of total calcium in the body is contained in the bone and less than one per cent in the blood and extracellular fluid (50). Fifty to 75 per cent of the calcium in the blood is diffusible while the rest is bound to protein (51). Of the diffusible calcium in the plasma most is ionized and is physiologically active, while a small part is nonionized but diffusible.
It is the ionized calcium, which is physiologically active, in which we are interested. Saffran and Denstedt (52) have studied ionized calcium during the administration of citrate. They found that the restoration of ionized calcium was very rapid even with high elevations of plasma citric acid. Reductions of ionized calcium were almost impossible to detect. Other experiments have been carried out in which calcium was removed by lead phosphate, ethylene-diaminetetraacetic acid and oxalate, and the body rapidly compensated and returned the plasma calcium to normal limits (53). Actually, the rate of calcium mobilization is directly proportional to the lowering of serum calcium. Since bone represents the greatest store of calcium, mobilization of calcium is limited by blood flow to the bone (54). Depressed ionized calcium is rapidly restored to normal, since the equilibrium between plasma ionized calcium and bone calcium is governed by the mass action law. Thus, if any factor tends to decrease the amount of ionized calcium present in the plasma, there is a tendency for more calcium to be mobilized from bone. In the presence of elevated citric acid it is possible to have a normal ionized calcium level in the presence of an elevated total calcium.

Krautwald and Dorow (55) have reported the results of infusion of sodium citrate in conscious human volunteers. They produced prolongation of the QT interval, occasional tetany and clouding of consciousness. Total plasma calcium was not reduced during tetany; but the administration of calcium chloride immediately counteracted the symptoms produced by the sodium citrate infusion. Chang and Freeman (56) observed an increase in plasma total calcium when sodium citrate was infused into dogs. An increase in total calcium in humans receiving ethylene-diaminetetraacetic acid has also been reported (57). In an effort to corroborate these results, commercially available acid citrate dextrose solution was administered at rates of 6.3 to 8.6 mg./kg./minute to three patients anesthetized with thiopental, nitrous oxide and oxygen (19). This is analogous to administering approximately 20 pints of blood per hour. In all three patients, there was a marked increase in the plasma citric acid level, the peak of which coincided with the termination of acid citrate dextrose administration. At no time was there any sign of tetany or hypotension, although there was prolongation of the corrected QT interval as determined by the electrocardiogram. At the same time there was an increase in the serum calcium and potassium levels. Return of the patients' serum calcium level to their pre-experimental level coincided with return of the plasma citric acid value to almost normal. It should be emphasized that, except for prolongation of the QT interval, no other premonitory signs have been observed with massive blood replacement as warning of the development of ventricular fibrillation or cardiac asystole.

The other facet of citric acid intoxication—the development of oozing—was studied by Zucker et al. (18) in a series of 77 patients.
Eighteen of these patients, studied during anesthesia and surgery, developed clinical evidence of vascular oozing. Extensive clotting studies were obtained at the same time. Plasma citric acid levels in these patients who were oozing varied from 7.9 mg. per cent in a patient who received 30 units of bank blood to 1.3 mg. per cent in a patient who had received no blood. There was no direct correlation between plasma citric acid levels and oozing. All instances of vascular oozing could be accounted for by changes in the clotting factors per se.

Although we have been unable to demonstrate citrate acid intoxication clinically, there are situations in which it might occur. These conditions are any factor that might interfere with the body's metabolism of citric acid, hypothermia which will decrease the rate of citric acid metabolism, long-standing liver disease with avitaminosis, saturation of enzyme systems, hypoparathyroidism and osteoporosis when calcium cannot be mobilized from the bone. Children, especially the newborn, may not have adequate calcium stores to draw upon, and therefore, may show signs of hypocalcemia. Shock could also conceivably contribute to "citric acid intoxication" because of failure of adequate circulation to the bone which is vital to the maintenance of calcium homeostasis.

The treatment of the complications of massive blood replacement does not require extensive electrolytic or hematological investigations. Accumulated knowledge suggests that the application of a few principles of prevention and treatment will prevent mortality from the cardiovascular complications of large amounts of bank blood. Preventive measures which have been found helpful at Memorial Hospital are: (1) adequate blood replacement as it is lost, (2) the use of an operating room electrocardiograph, (3) administration of a plasma volume expander when electrocardiographic changes occur, and (4) the administration of calcium gluconate or calcium chloride as indicated for the conditions listed in the previous paragraph.

Adequate blood replacement as it is lost will prevent circulatory collapse, which will result in the necessity of administering large quantities of blood in a short period of time. This may be done by estimation of the blood loss, both gravimetrically (weighing of sponges) and volumetrically, by measuring the blood in the suction bottle. The electrocardiogram will warn of impending ventricular fibrillation or cardiac asystole. Premonitory signs are bradycardia, peaking of the T waves, prolongation of the QT interval and distortion of the QRS complex. At this time the plasma volume expander is used to dilute the effect of the administered bank blood. The plasma volume expander does not contain potassium or citrate and is administered at room temperature. Usually the administration of one or two pints of plasma volume expander or saline will result in reversion of the electrocardiogram to normal. Additionally, prompt recognition of the appearance of ventricular fibrillation by means of the electrocardio-
gram facilitates immediate initiation of appropriate therapy. The administration of calcium gluconate or calcium chloride to revert the electrocardiogram to normal has not been uniformly successful in our hands. Since the cardiac action of excess calcium in some ways resembles that of digitalis (58), we use calcium gluconate during massive blood replacement only in cases of shock, in children, or in patients with defects in calcium metabolism.

The coagulation changes which occur with massive transfusion have been found to be defects of prothrombin, accelerator globulin, labile factor, fibrinogen, thrombocytopenia and fibrinolysis. A detailed hematological investigation in the case of vascular oozing during operations is not necessary. It is of great value, however, in the treatment of patients who ooze postoperatively. It has been our experience that oozing will usually stop with either the cessation of the surgical trauma after the wound is closed or by the administration of lyophilized plasma (antihemophilic plasma). Conditions which do not respond to the administration of lyophilized plasma or the cessation of surgery can usually be corrected by the administration of fresh whole blood drawn in plastic containers. This blood will contain adequate fibrinogen, platelets and prothrombin precursors. We have not had to treat platelet deficiencies with special platelet preparations or extracts at this time. Fibrinolysis usually responds dramatically to the administration of antihemophilic plasma.

Treatment of "citrate intoxication" postulates the existence of citrate intoxication. It is our belief that in normal patients who have not exhibited any shock, citrate intoxication does not occur. The defects described for the cardiovascular and coagulation systems of the human body during massive blood replacement can explain the complications previously ascribed to citrate intoxication.

REFERENCES