As the title implies, massive transfusion is not without risks—though the need for such treatment is regularly evidenced. The authors detail the changes which occur in the blood during the process of its being drawn, anticoagulated, and stored. The clinical significance of these changes and other complications are presented, along with their manifestations and treatment. Finally, a rational approach to the prevention of such complications is provided.

"Massive transfusion of whole blood has become more frequent over the past 30 years. Adams¹, in 1944, considered the infusion of 1,500 ml of blood a 'massive transfusion'.”

Improvements in blood banking have made enormous quantities of blood readily available. Rapid evacuation of the severely wounded from the battlefields and injured civilians has brought large numbers of patients with severe hemorrhagic shock to medical facilities where blood is readily available.

Open heart surgery using extracorporeal circulation, radical cancer surgery, and aggressive surgical intervention into massive hemorrhage produced in gastrointestinal and hepatic disease has created tremendous demands for blood replacement in the operating room. Today’s concept of “massive transfusion” has expanded to denote a replacement of half of the patient’s estimated blood volume in one hour.²

The transfusion of large amounts of blood is accompanied by a significant increase in patient mortality. Darby³ has shown that adult patients receiving 20 units of blood have a mortality of 50 per cent, while it can become higher if more blood is used.

Much of the mortality is due to the basic disease for which the blood is given. The patient with multiple traumatic lesions will not survive as well as the patient with a rather simple surgical operation. Yet, a certain amount of the mortality is due to changes which occur in the blood during the process of its being drawn, anticoagulated, and stored. These changes are usually referred to by the name “storage lesions.”

Most storage lesions, although usually minor in small transfusions, are greatly intensified when many units of blood are replaced over a short period of time. While simultaneously, the body’s capacity to correct these changes may become overbalanced. Some of these changes are either preventable or reversible, and therefore can be avoided if the practitioner knows what occurs and how to remedy the situation. These complications will be examined in this article.

Acid citrate dextrose (ACD) solution, formula B, until recently, has been the most widely used preservative-banked blood. The sodium citrate functions as an anticoagulant by chelating the ionized calcium. Citric acid is added to buffer the pH at 7.0, slowing metabolism and prolonging storage life. The viability of
the red blood cells (RBC's) is extended by the incorporation of dextrose as a metabolic substrate. Blood is stored at 4°C for a maximum of 21 days.

Now, the citrate-phosphate-dextrose anticoagulant is becoming more popular. In this preservative, the sodium citrate and citric acid are used to remove the calcium, but are present in smaller amounts. Monobasic acid phosphate is used to stabilize the pH at a higher value, and the amount of dextrose is comparable. Blood drawn in this solution exhibits a decreased storage lesion in almost all values studied (see Table 1), and the survival of the red cells is better than 70 per cent after 28 days of storage. Currently, the Bureau of Biologics of the Food and Drug Administration has approved this anticoagulant as acceptable for only 21 days, although it is hoped that this time will be extended to the more scientifically valid dating.

The biochemical aspects of the storage lesion are summarized in the following table:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Normal</th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.2</td>
<td>7.0</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Hgb (plasma) (mg %)</td>
<td>5</td>
<td>4</td>
<td>10</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>3.5</td>
<td>3</td>
<td>10</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Na (mEq/L)</td>
<td>140</td>
<td>150</td>
<td>148</td>
<td>145</td>
<td>142</td>
</tr>
<tr>
<td>Lactic acid (mg %)</td>
<td>10</td>
<td>20</td>
<td>70</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>PO₄ (mg %)</td>
<td>3.5</td>
<td>3.6</td>
<td>3.6</td>
<td>4.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Dextrose (mg %)</td>
<td>100</td>
<td>330</td>
<td>280</td>
<td>240</td>
<td>220</td>
</tr>
<tr>
<td>Ammonia (mg %)</td>
<td>0.05mEq/L</td>
<td>0.5mEq/L</td>
<td>.23mEq/L</td>
<td>.45mEq/L</td>
<td>.62mEq/L</td>
</tr>
</tbody>
</table>

However, a mixture of blood with ACD solution, and to a less degree CPD, with prolonged storage at 4°C renders the blood:

1. Acidotic (metabolic and respiratory).
2. Hypocalcemic.
3. High in citrate.
5. Hypothermic.
6. Hyperammonemic.

Further defects produced are:
1. Labile coagulation factor depletion.
2. Platelet depletion—in function and number.
3. Red blood cell swelling with diminished viability.
4. Decreased 2,3—DPG levels producing an increased affinity of hemoglobin for O₂ (shift to left of hemoglobin dissociation curve).
5. Micro aggregates of platelets, leukocytes, and fibrin debris.

Other dangers associated with blood transfusion are the transmission of hepatitis, syphilis, malaria, and cytomegalovirus. Lastly, the likelihood of a transfusion mismatch is vastly increased by the number of units infused and by the haste and confusion that often accompany emergency situations.

Let us consider some of these storage lesions in detail.

**Acidosis**

The in vitro metabolic acidosis produced by a mixture of fresh blood with ACD solution (pH 7.0) is magnified by accumulation of fixed and volatile acid metabolic products. The average unit of stored blood has a pCO₂ of 152–210 mmHg with a standard bicarbonate of
1.2–7.8 mEq/L. Storage also prevents the loss of lactic and pyruvic acids.

Clinically, adults tolerate this acid load well, even if rapidly administered. Howland suggests the administration of 44.6 mEq/L of sodium bicarbonate per 5 units of blood transfused to counteract the acute metabolic acidosis of transfusion. In hypothermic patients suffering from shock, this seems especially important, since they usually have preexistent metabolic acidosis secondary to stagnant tissue hypoxia and are less able to compensate. Most patients who survive hemorrhagic shock and massive transfusion develop a metabolic alkalosis postoperatively which is maximal on the third day. This is caused by the metabolism of the citrate preservative and the formation of excess bicarbonate. Patients whose shock is irreversible and whose liver function is inadequate do not develop this alkalosis.

Miller prospectively studied battle casualties requiring massive transfusion and found no correlation between the amount of blood transfused and the resultant metabolic acidosis both in patients in severe shock and those who were not. They found a marked variability in patient response and advised bicarbonate be used only when metabolic acidosis existed with a base excess of −7 or greater. Cloutier showed similar results.

Children represent a special circumstance. In neonates and infants, Schroeder advises routine replenishment of bicarbonate, using 1 mEq/L per 100 ml of infused blood, since they have a low standard bicarbonate and are less able metabolically to handle an acid excess.

The large load of dissolved carbon dioxide makes adequate ventilation essential.

Citrate intoxication and hypocalcemia

Citrate is rapidly metabolized by the liver to produce bicarbonate. The development of toxic levels in patients depends on very rapid infusion, with impaired liver function secondary to either preexistent liver disease, hypothermia, or shock. The toxic effects of citrate are coagulopathy and myocardial depression. The myocardial depression seems, in part, related to the depression of ionized calcium, as calcium replenishment can reverse the effects.

The intoxication syndrome consists of hypotension with adequate fluid replacement, electrocardiography changes of Q-T prolongation and T-wave depression and tetany. That these complications rarely occur suggests the body has enormous capacity to metabolize citrate and mobilize bony calcium. It is felt by most investigators that cardiac irregularities would predominate before calcium levels would be low enough to produce coagulopathy.

Prior to 1964, routine calcium replacement was a common practice until Howland reported a significant reduction in operative mortality attributed to massive transfusion when prophylactic calcium infusions were eliminated. He reasoned that the risk of cardiac arrest from the irritative effects of a sudden rise in calcium was far more significant than the risk of “citrate intoxication.” Large doses of intravenous calcium will produce premature ventricular contractions, ventricular tachycardia, and nodal blockade.

Schroeder concurs with Howland that calcium replenishment in adults is unnecessary and dangerous; but, is of the opinion that it is essential in neonates and infants, as they have an inadequate calcium store and their citrate metabolism is impaired. He advises that cautious prophylactic use of 1 ml of 10 per cent calcium chloride (1.8 mEq/L) for the first 100 ml of blood infused followed by 0.75 ml per 100 ml thereafter.

Parenthetically, the calcium chloride should be given either in a separate intravenous injection or else the blood administration line should be rinsed with about 10 ml of saline before and after the addition of the calcium. If this
is not done, some of the blood may clot at the interface between the blood and calcium.

Hyperkalemia
The plasma potassium concentration of a unit of stored blood rises from physiologic levels when just drawn to 25-35 mEq/L at 21 days. Concomitantly, the red cell mass loses this same potassium by hemolysis of some red cells and by a loss of intracellular potassium to the surrounding medium.

If hyperkalemia occurs, the electrocardiographic changes seen are tall symmetric peaked T-waves which suggest moderate elevation, while severe elevations of potassium produce atrial standstill and idioventricular rhythm with wide, slurred, bizarre QRS complexes.

When suspected, hyperkalemia should be treated vigorously by methods which cause potassium to return to the cell. One liter of an infusion of 10 percent dextrose containing 50 units of regular insulin, and alkalinization with sodium bicarbonate may cause such a potassium shift. Calcium will oppose the cardiotoxic effects of potassium and can be infused as 1-2 gms of calcium gluconate. One must avoid the simultaneous administration of sodium bicarbonate and calcium gluconate as insoluble calcium carbonates are produced.

Therapeutic efficacy can be followed by the disappearance of the signs of hyperkalemia under electrocardiography. Normally, hyperkalemia should not occur. If red cells are given rather than whole blood, the potassium rich plasma has been removed, and can produce no effect. Further, red cells are potassium deficient, and absorb some of the free potassium in the process of equilibration.

Hypothermia
This is the most significant “storage lesion.” Not only does it produce direct deleterious effects, but it obtunds the recipient’s ability to correct other storage lesions. Regardless of the amount of cold blood infused, the patient’s ability to maintain his temperature is hampered by the depressive effects of general anesthesia and the large heat loss from evaporation at the respiratory tract and surgical field.

Boyan demonstrated a relation in the massively transfused patient between the rate and amount of cold blood infusion and the incidence of cardiac arrest. In a group of patients receiving 3000 ml or more of cold ACD blood at 50 ml/min. or more, he noted 21 cardiac arrests in 36 subjects. With blood warmed to 30-35°C and transfused into a similar group of patients at comparable rates, there was only one cardiac arrest in 45 patients.

Hypothermia causes death acutely by producing ventricular fibrillation at temperatures below 30°C or by causing cardiovascular collapse. Boyan found the esophageal temperature of patients dying of cardiac arrest from hypothermia to be 27.5-29°C.

Hypothermia is a generalized metabolic depressant. Citrate metabolism is decreased 40 percent at 30°C. Metabolic acidosis is caused because peripheral circulatory depression is greater than metabolic slowing.

Boyan’s method of blood warming was via inline coils in a 30-35°C water bath. Blood must not be warmed more than 40°C as lysis of the red cells will occur. Recently, microwave ovens have been developed which can rapidly and safely warm a whole unit of blood when stored in plastic bags. These must be used with care. The heating action has no limit control, and therefore, can overheat. Several reports have been made where blood has been hemolyzed by such a unit. But, with proper care, the unit can be safe.

Hyperammonemia
Ammonia and other nitrogenous metabolic products accumulate in stored blood. These substances can potentially achieve high blood levels in hypothermic patients with acute or chronic liver imm...
pairment. These products could contribute to postoperative obtundation in patients with preexistent liver disease.

Coagulopathies

One of the most vexing problems to occur during massive transfusion is the appearance of uncontrollable oozing from all cut surfaces. This coagulopathy can have many causes; here are the most common.

Thrombocytopenia. This is the most usual source of coagulation difficulty. Not only do platelets disappear from stored whole blood, but those remaining lose their function so rapidly that blood stored more than six hours is relatively ineffective in correcting thrombocytopenia. Oberman feels that a unit of blood must be less than six hours old if it is to deliver adequate viable platelets.

Roy has shown that separation of platelets from whole blood extends their life. His team demonstrated substantial increases in platelet concentration stored at 4°C and at 22°C.

Miller has shown that excessive surgical bleeding was related to the absolute platelet count. No patients in his series had coagulopathies if platelet counts exceeded 100,000/mm³, but all had excessive bleeding if counts were less than 50,000/mm³.

Platelet function can be clinically assessed in all emergencies by observing the quality and retraction of a fresh blood clot and the count can be approximated from a Wright stained smear of fresh blood (less than one platelet per oil immersion high power field is equivalent to a platelet count of less than 50,000/mm³). But, this method is crude and relatively inaccurate. Any patient who is bleeding after surgery should have his platelet count determined. With the new electronic equipment available, it is simple to do the count and takes only a short time.

Treatment of platelet deficiency depends on how actively the patient is bleeding. If large amounts of red cells are being lost, blood less than six hours old is the treatment of choice if it is available. If not available, red cells and platelet concentrates can be substituted.

If the patient is only oozing, the thrombocytopenia can be corrected by infusion of platelet concentrates. One should expect one platelet concentrate to raise the platelet level in a 150-pound patient about 8,000/μl. Therefore, therapeutic dosage of platelet concentrate is normally 6-8 packs every two days if there is no more active bleeding.

Coagulation factor deficiencies. Factors V and VIII are the only labile coagulation factors in stored blood. Concentrations fall to 50 per cent of normal within three days of storage at 4°C. The other factors are stable within the three-to-four weeks shelf life of the blood unit. Usually, a 70 per cent depression of these factors is needed before a coagulopathy develops; but, in the presence of massive trauma, bleeding may occur at higher levels.

Diagnosis of these deficiencies is based upon the patient's history, a prolonged partial thromboplastin time, and usually a prolonged prothrombin time. The medical history will tell if this patient is a known hemophiliac, has had anticoagulant therapy, has Christmas Disease, or has some acute form of hepatitis. If the partial thromboplastin time is prolonged, laboratory studies should be carried out to identify the factor deficiency, even though this information may not be available when therapy is instituted. Lacking these baseline studies, one may not know how to direct and adapt the therapy if the initial treatment of the bleeding is unsuccessful.

Disseminated intravascular coagulation (DIC). Simmons found that coagulation disorders in combat casualties were seldom serious when related to thrombocytopenia or factor deficiencies, but profound and often only partially reversible when a consequence of DIC. Studying the coagulation parameters of battlefield evacuees in profound shock, Simmons found that they develop acutely a hypercoagulable state probably related.
to elevated catecholamines and adrenal steroids. This is reflected in a shortened prothrombin time, partial thromboplastin time and clotting time, as well as an elevation of fibrinogen.

As shock continues, prolonged prothrombin time decreases, pH and prolonged clotting develops, as well as a depression of platelets and fibrinogen occurs. A bleeding diathesis occurs if such depressions are severe. Shock and tissue destruction with cell lysis and hemolysis initiate this syndrome. This type of coagulopathy may develop in the face of a massive transfusion, though, it is not directly related to it.

The diagnosis is further substantiated by a prolongation of all coagulation parameters, depression of all clotting elements as they are “consumed” in the DIC, and an increase in fibrin split products. It is reversed only through treating the predisposing factors and giving therapeutic doses of heparin to prevent further clotting.

Yet another cause of DIC directly related to transfusion is gross mismatch resulting in a hemolytic transfusion reaction. Such reactions occur in 1:1,000 to 1:10,000 transfusions, and 25 per cent are associated with a bleeding diathesis. The intravascular coagulation is initiated by the release of RBC thromboplastin. The individual with adequate tissue perfusion tolerates this insult well, but the post-surgical patient in profound shock with a decreased microcirculation has a high risk of developing DIC.

Though fibrinolysis may play a role in this coagulopathy, antifibrinolytic agents must never be administered unless lysis of an adequate clot can be seen to occur within one hour and a trial of heparin has been attempted. Inappropriate administration of Amicar® (aminocaproic acid) is disastrous, especially in a patient with DIC in profound shock.

Defective O₂ transport

Valtis and Kennedy demonstrated that a decreased O₂ delivery capacity of stored blood related to a shift of the O₂ dissociation curve of hemoglobin to the left. Bunn demonstrated that this defect was related to a marked depletion of RBC 2-3 diphosphate glyceride. The defect corrects spontaneously in vivo after several hours or can be corrected in vitro by the addition of the nucleoside, inosine, to the storage medium. The partial pressure of O₂ at 50 per cent hemoglobin saturation at 38°C is 26.7 Torr; but with seven or more days of acid citrate dextrose storage, the pressure is only 17 Torr.

This deficiency can only worsen tissue hypoxia and emphasizes the need for a high fraction of inspired oxygen (FIO₂). Miller states that only the blood drawn in ACD and stored less than three days can deliver O₂ at levels approaching normalcy. This time would be increased if the anticoagulant used was CPD.

Huggins demonstrated the inferiority of old stored blood by producing hemorrhages in rats and replacing their blood loss with old blood. Animals replenished with old blood demonstrated the lowest survival rates, fresh blood the highest. Not until the old blood brought the hematocrit to 60 per cent (normal of 40 per cent) was old blood as effective as fresh (100 per cent survival).

Dr. Huggins concluded, “recipients of large-volume transfusion, particularly patients with cardiopulmonary disease, should receive fresh or freshly frozen blood cells. At our institution, we no longer accept blood older than ten days from outside sources.”

Microembolization

“Shock lung,” manifested as an edematous noncompliant lung with a profound shunt, is a subject of much current interest. It has been suggested that this entity can be the consequence of the microembolic shower received by the lungs during massive transfusion. Microemboli are small platelet blood cells or fibrin aggregates which gradually accumulate as blood is stored and
which pass through the standard 170-
micron blood administration filters.

McNamara studied the “screen
filtration pressures” (SFP) of whole
blood. SFP is that pressure required to
force a standard flow through a stan-
dardized mesh with a 20 (μ) pore size
and fixed cross-sectional area. He found
that the SFP of bank blood increases
with storage and that it is related to
the accumulation of aggregated material.
By comparing a transfused patient’s in-
ferior and superior vena cava SFP’s with
arterial SFP and that of the infused
blood, he demonstrated that these parti-
cles were partially filtered by the lung
and the remainder were filtered by the
peripheral capillary bed. He was able
correlate the degree of postoperative
hypoxemia with the volume of blood
transfused.

Blood filters remove less clotted
material with each successive unit trans-
fused. Moseley and Doty demonstrated
that, after the third unit, a significant
amount of debris passes through the
filter. The embolization of this material
has been demonstrated by Jenevein and
Weiss.

**Diminished RBC survival**

Preservation injures red blood cells,
and the degree of injury is related to
the storage time. The injured red blood
cells are quickly removed by the liver
and spleen (10:1) with no release of
free hemoglobin within the first 24 hours
post-transfusion. Survival of those re-
main ing red blood cells is quite variable
and depends more on host factors than
on storage time.

Fresh blood less than 24 hours old
is completely viable in vivo. Thereafter,
the viable fraction decreases at approxi-
mately one percent per day. Twenty-one-
day-old blood preserved in ACD must
supply a minimum of 70 per cent viable
red blood cells with an average of 80
per cent. Blood preserved in CPD for
21 days will have an average red cell
survival of 85 per cent.

A certain amount of iatrogenic red
cell damage and diminished survival can
be produced by administering whole
blood of a compatible but not identical
blood group. For example, suppose
Group O blood is given to a patient who
is Group A. Although, the O red cells
will survive, some of the patient’s own
red cells will be destroyed by the Anti-A
in the Group O plasma.

Originally, the blood given was low
titered, but studies have shown that
the incidence of low titer donors in our
population is decreasing. Most of this
is due to the increase in the number of
immunizations being given. Immuniza-
tions against typhoid, tetanus, and
plague also increase the titer of blood
group antibodies. The surest way to
prevent destruction of red cells by trans-
fused blood plasma is to remove the
plasma and give the blood as red cells.

**Hepatitis**

Massive transfusion greatly magni-
fies the risk of developing viral hepato-
tis. The incidence of anicteric hepatitis
is 7.3-7.9 per 1000 units with commer-
cial blood and 2.5 per 1000 units with
volunteer donor blood. Furthermore,
the risk of hepatitis correlates well with
the incidence of the hepatitis antigen
HBAg in the donor population. In a
prospective study of open heart surgery
patients, the administration of 10 ml of
gamma globulin on the first, fourth, and
seventh postoperative weeks was found
to have no effect on the incidence of
hepatitis.

Currently, the best method of de-
creasing the incidence of post-transfu-
sion hepatitis is to test all donors for
the presence of HBAg and to use pri-
marily blood obtained from volunteer
donors.

**Conclusion**

In conclusion, the storage lesions
of bank blood and their clinical signi-
ficance have been presented along with
their manifestations and treatment.
Other complications of massive blood
replacement have been discussed.

A rational approach to the preven-
tion of complications in transfusion suggest the following:
1. Warm the blood and the patient.
2. Administer bicarbonate and calcium cautiously and prophylactically to infants and children, but to adults only when specifically indicated.
3. Administer as fresh blood when it is available.
4. Maintain high inspired O₂ concentrations.
5. Change blood administration sets frequently.
6. Be compulsive about checking that blood is appropriately crossmatched.
7. Monitor an electrocardiogram or cardio scope for signs of electrolyte disturbance (specifically calcium and potassium).

If a bleeding diathesis occurs, draw blood for a study of partial thromboplastin time, prothrombin time, platelet count, fibrinogen levels, and fibrin split products. The laboratory should be immediately informed of the problem so that they may check the accuracy of the crossmatch and also may rush the desired tests. The bleeding can usually be stopped temporarily by the infusion of blood drawn less than 24 hours previously. By the time this is infused, the laboratory results should be available, and definitive component therapy can be instituted.

REFERENCES
AUTHORS

Maurice Lippmann, MD, is Associate Professor of Anesthesiology at the University of California, Los Angeles, School of Medicine. He is Division Chief of Cardiovascular Anesthesia at the school’s affiliate, Harbor General Hospital in Torrance, California. Born in New York City, Dr. Lippmann received his MD from the University of Munich in Germany. He interned at Washington Hospital Center in Washington, D.C., and at Cedars of Lebanon Hospital in Los Angeles, California. His residency in anesthesiology was completed at Harbor General Hospital. Dr. Lippmann became Staff Anesthesiologist there in 1964. He has authored numerous articles on anesthesia for both American and European medical publications.

Byron A. Myhre, MD, PhD, is Professor of Pathology and Head of Immunopathology at the UCLA School of Medicine in Los Angeles, California, and Harbor General Hospital in Torrance, California.