Massive blood transfusion may be defined either as the acute administration of more than 1.5 times the patient's estimated blood volume [36], or as the replacement of the patient's total blood volume by stored homologous bank blood in less than 24 h [18]. The purpose of this review is to provide the reader with a practical approach to the initial management of the acutely bleeding, hypovolaemic patient, together with a description of some of the newer agents and techniques now available to treat major haemorrhage.

Acute haemorrhage leading to acute hypovolaemic shock is a medical emergency carrying a high mortality and therefore requires prompt and effective treatment. Initial management includes rapid restoration of the circulating blood volume, correction and maintenance of adequate haemostasis, oxygen delivery and colloid osmotic pressure and correction of any biochemical abnormalities. The investigation and treatment of the underlying cause of bleeding should also be undertaken as soon as possible (table I).

In addition to blood loss, hypotension may result from other coexisting causes that require treatment. These include decreased ionized calcium concentration, development of arrhythmias, pre-existing cardiac disease, sepsis (causing vasodilatation), air embolism, hypothermia and immunological reaction to drugs.

RESTORATION AND MAINTENANCE OF CIRCULATING BLOOD VOLUME

The rapid and effective restoration of an adequate circulating blood volume (so that tissue perfusion and oxygen delivery are maintained) is crucial in the early management of major haemorrhage, as mortality increases with increasing duration and severity of shock.

Venous access and monitoring

Poiseuille's equation states that, for a Newtonian fluid under conditions of laminar flow, the resistance to flow is directly proportional to the length of the tube, the viscosity of the fluid and the pressure gradient, and inversely proportional to the fourth power of the radius. Under these conditions, doubling the radius increases the flow by a factor of 16, while shortening the length of cannula or reducing the viscosity of fluid has considerably less effect.

In the acutely hypovolaemic patient, at least two large-gauge i.v. cannulae should be inserted into appropriately sized veins, usually in the antecubital fossae. If peripheral venous access is difficult, a cannula may be inserted into a large, central vein such as the subclavian, internal jugular or femoral vein. Alternatively, a venous cutdown may be performed on the saphenous vein at the ankle.

When a massive transfusion is anticipated during surgery, at least two large-gauge venous cannulae (12-gauge) should be inserted, solely for transfusion purposes. In addition, an arterial cannula and triple lumen central venous catheter may prove useful, allowing rapid blood sampling and direct measurement of arterial and central venous pressures, respectively. The triple lumen catheter also provides access for intermittent bolus administration of drugs, or drug infusions. Alternatively (or in addition), a sheath introducer (8-French gauge) may be inserted into a central vein, so providing a large cannula for transfusion and a means whereby a pulmonary artery catheter can be inserted, when indicated.

Unless contraindicated by pelvic or urethral injury, a urethral catheter should be passed and urine output monitored hourly. In addition, central and peripheral temperatures should be recorded and pulse oximetry used (fig. 1).

Needles and sharp objects should be handled and disposed of carefully to avoid needlestick injury. The wearing of gloves is recommended to prevent contamination of the hands with spilled blood. The use of three-way taps (with or without extension

<table>
<thead>
<tr>
<th>Table I. Management priorities in massive transfusion (the exact priority depends upon the circumstances)</th>
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<tbody>
<tr>
<td>Restore circulating blood volume</td>
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<tr>
<td>Maintain oxygenation</td>
</tr>
<tr>
<td>Correct coagulopathy</td>
</tr>
<tr>
<td>Maintain body temperature</td>
</tr>
<tr>
<td>Correct biochemical abnormalities</td>
</tr>
<tr>
<td>Prevent pulmonary and other organ dysfunction</td>
</tr>
<tr>
<td>Treat underlying cause of haemorrhage</td>
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</tbody>
</table>

M. D. J. DONALDSON, M.R.C.P., F.R.C.A.N.E.S., G. R. PARK, M.D., F.R.C.A.N.E.S. (Department of Anaesthesia); M. J. SEAMAN, F.R.C.P. (Department of Haematology); Addenbrooke's Hospital, Cambridge CB2 2QQ.

Correspondence to G.R.P.
tubing) reduces the need to use needles for drug administration or blood sampling.

**Initial resuscitation: crystalloid or colloid?**

The success of initial resuscitation in the acutely hypovolaemic patient depends more upon speed and adequacy of repletion than upon which fluids are used, anaemia being tolerated better than hypovolaemia. However, the debate continues as to which is the best fluid for this initial resuscitation [11, 12, 19, 31, 40] and there have been no adequate controlled clinical trials comparing the outcomes in patients resuscitated either with albumin or with other colloid solutions (gelatins, dextrans or hydroxyethyl starch). Two facts are, however, not in dispute. First, about 50–75% less colloid than crystalloid is required to achieve a given end-point in blood volume expansion, but at an increased financial cost. The need to give more fluid when using crystalloids may increase the logistic difficulties of early resuscitation and result in greater thermal stress if the fluids are cold. Second, unlike crystalloids, colloids are associated with allergic reactions, albeit rarely.

In the majority of studies, the type of fluid administered did not influence outcome. It is not known, however, if there are any identifiable subgroups of patients in whom the choice of replacement fluid is important. Several such groups have been suggested including the elderly, those with low colloid osmotic pressures and poor wound healing, patients suffering from anaphylactic shock and those with non-cardiogenic pulmonary oedema. In practice, however, combined therapy using both colloids and colloids is often used and has been shown to produce better results in experimental shock models than the use of either colloid or crystalloid alone [45].

Colloid solutions decrease the concentration of clotting factors by haemodilution, but both hydroxyethylstarch and dextran reduce factor VIII concentration to a greater extent and both are incorporated into polymerizing fibrin fibres, resulting in large, bulky clots and enhanced fibrinolysis [48]. However, the degree to which the circulating blood volume can be replaced by plasma substitutes depends more upon the dilution of the cellular components of the blood than on its plasma components. Although somewhat arbitrary, a haemoglobin concentration of approximately 10 g dl⁻¹ (or a PCV of 30–35%) represents the threshold below which oxygen delivery is likely to be insufficient even when a large circulating blood volume and cardiac output are maintained. However, it is difficult to define specific concentrations below which transfusion of red cells becomes mandatory, and these values may be grossly misleading after acute haem-
orrage because they may not reflect the degree of blood loss for some hours.

**Measurement of blood loss**

During surgery, blood loss is traditionally estimated by weighing swabs and measurement of blood aspirated into the suction apparatus. In massive haemorrhage, the value of these methods is questionable, as a considerable amount of blood is inevitably spilled onto the drapes, floor and surgeons. In traumatized patients, further large loss of blood may also have occurred before arrival in hospital, or may be concealed in the limbs and pelvis at the site of fractures, or in the chest or abdomen. All this can result in an underestimate of the true blood loss, with consequent inadequate replacement. Rather than rely on these poor estimates of blood loss, patients should be transfused according to measured cardiovascular variables such as heart rate, arterial pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac output, oxygen delivery and oxygen consumption. The measurement of PCV and blood lactate concentrations may also be helpful.

**Blood selection and crossmatching**

At the first opportunity, blood samples should be sent urgently to the laboratory (table I), together with a warning of the urgent need for blood for transfusion. When unexpected major haemorrhage occurs and blood is required rapidly, uncrossmatched blood may be requested urgently (assuming the patient’s blood group is known and the presence of atypical antibodies has been excluded). Then, compatibility testing simply involves checking the ABO and D group of the units before transfusion. However, in cases where the blood group of the patient is not known, O Rhesus Negative blood may be infused initially, before changing to ABO-specific blood when the patient’s blood group has been identified.

If atypical antibodies are known to be present and major haemorrhage is anticipated, sufficient antigen-negative blood should be crossmatched in advance and reserved. However, if large supplies of antigen-negative blood are not readily available, it may be necessary to use only ABO-compatible blood during the massive transfusion period. The antigen-negative blood should then be given when the rate of blood loss has been substantially reduced.

An accurate record should be kept of the amount of blood and fluid given, including each unit number and blood group, as any transfusion reaction or transfusion-related infection requires identification and retrieval of the units responsible. In our experience, immunologically-mediated reactions to blood or blood products are rare. The reasons for this are not clear, but may be a result of the small concentrations of circulating antibodies and inflammatory mediators owing to their dilution. Nevertheless, ABO-incompatible haemolytic transfusion reactions are the most common cause of acute fatalities because of blood transfusion, and are likely to occur in the emergency setting because of clerical errors [20]. In addition, a haemolytic reaction may easily be overlooked in a critically ill patient or attributed mistakenly to other causes.

As there is often a conflict in priorities for the doctor’s attention in these circumstances, the task of checking and recording the fluids administered may be delegated to other theatre personnel or assistants. It is our normal practice for two people to check all blood when it first arrives in the operating theatre.

**Pressure bags, blood warming and rapid infusion devices**

The requirements of a transfusion system for the management of major haemorrhage include the ability to transfuse blood at fast flow rates (up to 500 ml min⁻¹) and at temperatures greater than 35 °C. One such system uses a constant pressure infusion device [23] combined with an efficient blood warmer (Grant B12) and a purpose-designed double-length blood-warming coil [46]. Efficient counter-current aluminium heat exchangers have been investigated under conditions of a high flow and found to be effective [4]. Priming or flushing blood through the system with fluids containing calcium (such as compound sodium lactate and Haemaccel) should be avoided, as this may result in blood clot formation in the tubing [3]. This results from the reversal, by calcium ions, of the anticoagulant effect of citrate. The gas bubbles seen in the warming coil when a blood warmer is in use result from release of dissolved carbon dioxide from the blood during warming, and usually are of no clinical significance.

The Haemonetics Rapid Infuser device (fig. 2) has a 3-litre reservoir into which cell-saved (see below) or banked blood and fresh frozen plasma can be stored, warmed and infused at rates of up to 2 litre min⁻¹ [42]. The system also incorporates a 40-μm high-flow blood filter, pressure sensor, air detector and heat exchanger, and can be prepared for use in about 3 min.

If such equipment for rapid transfusion is not available or cannot be used (i.e. with fluid stored in glass bottles), the speed of transfusion can be increased by simple manoeuvres. For example, increasing the height of the fluid above the patient or using intermittent manual compression of the lower chamber of the giving set when full of fluid (in such a way that the ball valve seals off the top inlet channel) are two such methods. Alternatively, using a large syringe and a three-way tap in line, fluid can be...

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**Table II. Baseline laboratory investigations in acute haemorrhage**

<table>
<thead>
<tr>
<th>Blood transfusion (10 ml clotted blood)</th>
<th>Group</th>
<th>Antibody screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology (2 ml in EDTA)</td>
<td></td>
<td>Compatibility testing</td>
</tr>
<tr>
<td>Coagulation (5 ml in citrate)</td>
<td></td>
<td>PCV</td>
</tr>
<tr>
<td>Biochemistry (5 ml in lithium heparin)</td>
<td></td>
<td>Urea and electrolytes</td>
</tr>
</tbody>
</table>

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**Baselvel laboratory investigations in acute haemorrhage**

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Coagulation</th>
<th>Haematology</th>
<th>Measurement of blood loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting screen</td>
<td>Haemoglobin</td>
<td>PCV</td>
<td>During surgery, blood loss is traditionally estimated by weighing swabs and measurement of blood aspirated into the suction apparatus. In massive haemorrhage, the value of these methods is questionable, as a considerable amount of blood is inevitably spilled onto the drapes, floor and surgeons. In traumatized patients, further large loss of blood may also have occurred before arrival in hospital, or may be concealed in the limbs and pelvis at the site of fractures, or in the chest or abdomen. All this can result in an underestimate of the true blood loss, with consequent inadequate replacement. Rather than rely on these poor estimates of blood loss, patients should be transfused according to measured cardiovascular variables such as heart rate, arterial pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac output, oxygen delivery and oxygen consumption. The measurement of PCV and blood lactate concentrations may also be helpful.</td>
</tr>
</tbody>
</table>
be drawn rapidly into the syringe from the giving set, before being administered to the patient through the three-way tap. Although no longer widely available, a manually operated Martin's rotary pump may be used. Its major disadvantage is that it tends to pull the administration set out of the infusion bag.

Intraoperative autotransfusion

Autotransfusion or autologous transfusion can be defined as the reinfusion of blood or blood products derived from the patient's own circulation. The main advantage of autotransfusion is that it avoids the complications associated with homologous transfusion, which include infection, febrile reactions, anaphylaxis, haemolytic transfusion reactions and immunosuppression. In addition, autologous blood may be the only option for some patients, especially those with rare blood phenotypes or those with rapid blood loss. It may also be acceptable to some patients on religious grounds who refuse transfusion of homologous blood. Autologous transfusion should also reduce the workload and conserve stocks in blood banks [28, 47].

Blood for reinfusion may be obtained from the patient either by preoperative donation or during operation by a process of blood salvage. Preoperative donation, involving either predeposit programmes or preoperative haemodilution, is an elective procedure and is not, therefore, of benefit in the management of unexpected major haemorrhage.

Intraoperative autotransfusion using an automated cell saver system such as the Haemonetics Cell Saver 4 (fig. 2) is of great value in decreasing the transfusion requirement for bank blood when a large blood loss occurs [9]. In addition, the blood is compatible, has normal red cell concentrations of 2,3-diphosphoglycerate, is already warm and is available quickly. During autologous transfusion with the Haemonetics system, blood aspirated from the surgical field is collected via double-lumen suction lines where it is mixed with anticoagulant solution (heparinized saline) and transferred to a reservoir. The blood is filtered, centrifuged and washed with saline before resuspension in saline and transfer to a reinfusion bag at a PCV of about 50%. The discarded supernatant solution contains debris from the surgical field, white blood cells, platelets, activated clotting factors, free plasma haemoglobin and anticoagulant. Three units of blood can automatically be processed in approximately 10 min, and the cell saver can be used in conjunction with the rapid infusor device (fig. 2) to supplement homologous transfusion if large blood losses are expected [Smith MF, unpublished observations].

However, although the disposable plastic software can be assembled quickly, technical help must be available in the operating theatre if the cell saver is to be used safely and efficiently. To minimize the infection risk, the time elapsing between the start of collection and reinfusion should not exceed 12 h. Relative contraindications to the use of the cell saver include blood contamination by bacteria, intestinal contents or tumour cells [8].

An alternative manual method of intraoperative blood salvage is the Solcotrans Autologous Collection System, although its capacity is limited. Blood is drained or sucked through a 40-μm blood filter into a specially designed reservoir containing acid citrate glucose; the anticoagulated whole blood is then reinfused.

Fig. 2. The Haemonetics Rapid Infuser Device (left) and Cell Saver (right).
Potential complications of blood salvage systems, include haemolysis, coagulopathy resulting from infusion of residual anticoagulant and dilution of coagulation factors and platelets, hypocalcaemia (when citrate is used) and air embolism.

**Aetiology**

In situations other than those of liver transplantation and in patients with a pre-existing coagulopathy, it is unusual for a significant reduction of plasma coagulation factors to occur solely as a result of massive transfusion of stored whole blood [7,37]. Stored whole blood contains adequate amounts of coagulation factors I, II, VII, IX, X, XI and XII. Concentrations of factors V and VIII are reduced in stored blood, although these may be adequate for haemostasis [39] (the critical concentration of factor VIII is generally considered to be 35% of the normal plasma concentration). Furthermore, factor VIII is an acute phase protein and the stress of surgery and trauma increases its rate of production. Nevertheless, dilutional coagulopathy can be expected when replacement therapy has largely consisted of fluid containing no coagulation factors, red cell concentrates or red cells suspended in additive solutions. Therefore, after the first 4 u of a massive transfusion, it is advisable to use whole blood (preferably less than 7 days old) in order to maintain haemostasis and colloid osmotic pressure and so reduce the requirement for fresh frozen plasma (FFP). Whole blood that has been stored for 2 or 3 days is devoid of functioning platelets, although some have suggested that significant platelet function persists for longer than this [32]. A massive transfusion leads to a decrease in platelet count, but not to the concentrations predicted by the washout curve in a blood exchange model [7,37]. There seems to be a considerable reserve of platelets which can be synthesized or released rapidly from the spleen and marrow into the circulation when required.

The diffuse pathological bleeding that sometimes develops in patients receiving a massive transfusion is not therefore caused primarily by dilutional effects, but probably has many causes (table III). Clinically, microvascular bleeding produces oozing from the mucosae, raw wounds and puncture sites, together with generalized petechiae and an increase in size of contusions. Disseminated intravascular coagulopathy (DIC), leading to thrombocytopenia and a reduction of plasma coagulation factors, may also occur in up to 30% of patients during a massive transfusion [34]. It is a complication of shock and inadequate or delayed resuscitation (leading to hypoperfusion) or of the surgery itself (with release of tissue thromboplastin). Physiological changes such as the development of metabolic acidosis, hypothermia, hypocalcaemia and hypokalaemia exert adverse effects on coagulation which improve when they are corrected. In summary, it is primarily the disease itself (hypoperfusion) and not the treatment (transfusion) that causes the coagulopathy in these patients [7,27,37].

In patients with severe liver disease, the pre-existing coagulopathy consists typically of a decrease in platelet count (caused by hypersplenism and a decreased platelet survival time) and in all coagulation factors except factor I and V (because of a decrease in the synthetic ability of the liver). These deficiencies lead to a prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT). If the coagulopathy is severe it may require correction with platelets and fresh frozen plasma in the period immediately before operation to facilitate safe insertion of intravascular monitoring catheters and to reduce bleeding during the operation.

Platelet dysfunction is the major haemostatic defect in patients with uraemia. They may benefit from treatment with desmopressin (see below), as will patients with haemophilia A and von Willebrand's disease.

**Monitoring of coagulation and replacement therapy**

In the past, standardized guidelines for the administration of platelet concentrate (PC) and fresh frozen plasma (FFP) have been used. These included the administration of FFP 2 u for each 10 u of blood transfused and PC 6 u for every 20 u of blood [13]. However, there are no controlled studies showing a clinical benefit from these regimens and they carry increased risk associated with pooled blood component administration, together with an increased cost. Therefore the need for FFP, PC and specific coagulation factors should, whenever possible, be established by laboratory evidence of a deficiency (table IV).

While delays in acquiring the results of laboratory tests pose a formidable problem, coagulation can be monitored in the operating theatre using an *in vitro* determination of whole blood clotting time, such as the Hemochron System. This measures the activated clotting time [16,43] and was designed primarily for monitoring heparin therapy. It is less sensitive and less specific in diagnosing plasma coagulation factor deficiencies than the PT or the APTT. However, rapid estimation of the trends in PT and APTT can now be obtained in theatre using the Ciba Corning 512 coagulation systems [Luddington RL, Smith MF, unpublished observations]. Others have demon-

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**Table III. Causes of coagulopathy after massive blood transfusion**

<table>
<thead>
<tr>
<th>Pre-existing defects, caused by the underlying disease or drugs used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilution by replacement therapy</td>
</tr>
<tr>
<td>Artificial plasma expanders, e.g. dextran and hydroxyethyl starch</td>
</tr>
<tr>
<td>Stress</td>
</tr>
<tr>
<td>Tissue injury</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Bacteraemia</td>
</tr>
</tbody>
</table>

**Table IV. Basic screening tests for bleeding after operation**

| Platelet count |
| Prothrombin time |
| Activated partial thromboplastin time |
| Plasma fibrinogen concentration |
| Fibrinogen degradation products, when indicated |
strated the diagnostic value of thrombelastography in operations such as liver transplantation [26].

An increase in the PT and APTT to more than 1.5 times the upper limit of normal correlates with clinical coagulopathy and justifies the use of FFP, providing a coagulopathy is evident clinically. FFP should then be given rapidly and in adequate quantities, 4 u (800 ml) being the usual amount for an adult. The role of platelet counts in the management of massive transfusion remains controversial. Confirmation of thrombocytopenia (platelets < 50 \times 10^3 \text{ litre}^{-1}) should probably be sought in addition to clinical evidence of microvascular bleeding, before the administration of platelets. A standard adult dose is PC 6–8 u (concentrate 1 u/10 kg body weight). Ideally, ABO and Rhesus-specific PC should be used and given preferably via a platelet administration set, although a standard blood administration set suffices.

Laboratory tests of coagulation are useful in the diagnosis of abnormal haemostasis and in directing therapy and monitoring its effects, but used alone cannot determine the need for transfusion of PC or FFP. Marked abnormalities in laboratory tests may be present without clinically abnormal bleeding and, in these situations, PC and FFP should be withheld until the coagulopathy becomes clinically evident, unless substantial blood loss is expected to continue [14]. Conversely, when inadequate coagulation is clinically evident, the need to transfuse PC or FFP may precede the availability of laboratory confirmation. However, there is no place for the prophylactic use of PC or FFP in massive transfusions.

The diagnosis of disseminated intravascular coagulation (DIC) can be made usually by establishing substantial increases in PT, APTT and fibrinogen degradation products (FDP), together with a markedly decreased platelet count and fibrinogen concentration. During large transfusions, the distinction between DIC and dilutional coagulopathy hinges upon the demonstration of an increased concentration of FDP and the finding that laboratory abnormalities are disproportionately greater than those expected from haemodilution alone. In general, the best treatment of DIC is to remove the cause but, once established, FFP, PC and cryoprecipitate (as a source of fibrinogen) are often needed.

"Fresh" whole blood, although theoretically useful in preventing or treating a coagulopathy, is rarely available because of the time needed for collection, grouping, compatibility testing, microbiological screening and transport. In practice, it has no advantage over the use of stored whole blood or red cell components combined with FFP and PC.

**Adjunctive techniques and pharmacological therapy**

A variety of techniques have been used in certain circumstances to control bleeding temporarily. These include packing of body cavities, the placement of a Sengstaken–Blakemore tube and the use of medical antishock trousers [41].

Additional drug therapy may also be beneficial in the bleeding patient in some situations. For example, desmopressin ([1-deamino, 8-d-arginine] vasopressin) is a synthetic analogue of vasopressin and alters coagulation by its effects on circulatory endothelial cells and platelets. It may prove useful in patients with Haemophilia A, von Willebrand’s disease and uraemia [21]. Potential complications resulting from its use include a decrease in free water clearance, hypotension or hypertension, and thrombosis.

Antifibrinolytic agents (such as tranexamic acid) bind to plasminogen and plasmin and interfere with their ability to split fibrinogen. Patients with normal haemostatic function who bleed excessively after prostate surgery (by release of tissue plasminogen activator from prostatic tissue) may benefit from antifibrinolytic therapy. Cardiopulmonary bypass is commonly accompanied by fibrinolysis, and antifibrinolytic therapy appears to decrease bleeding without increased risk after cardiac surgery [22]. The anhepatic phase of liver transplantation is similarly associated with increased fibrinolytic activity, and antifibrinolytic therapy has been shown to be beneficial in these patients [25]. Potentially undesirable effects of these agents include increased risk of systemic thrombosis, and patients with bleeding in the kidneys or ureters may fill the upper urinary tract with thrombus. DIC is also a contraindication to antifibrinolytic therapy.

Aprotinin (Trasylol) is a serine protease inhibitor which has been shown to decrease blood loss during cardiac surgery [2] and liver transplantation [33,38], although its mechanism of action in these situations remains unknown. Allergic reactions and renal toxicity arouse concern about its clinical safety.

**CORRECTION OR PREVENTION OF BIOCHEMICAL ABNORMALITIES**

**Citrate toxicity and decrease in ionized calcium**

Each unit of blood contains approximately 3 g of citrate as anticoagulant. In normal circumstances, this is metabolized rapidly by the liver, and transfusion rates of blood in excess of 1 u every 5 min or liver function must be impaired before citrate metabolism becomes overwhelmed. Bunker, Bendixen and Murphy [5] infused sodium citrate into six anaesthetized humans and nine anaesthetized dogs. At the plasma concentrations of citrate they observed (which were similar to those during massive blood transfusion in both dogs and humans: 2–4 mmol litre$^{-1}$), both cardiac output and arterial pressure decreased by up to 40% because of myocardial depression.

The decrease in myocardial function is caused by citrate binding to the ionized calcium fraction in blood. This reduces the amount available for the normal physiological actions of calcium. The clinical manifestations of citrate intoxication are those of hypocalcaemia: hypotension, small pulse pressure and increased diastolic and central venous pressures. However, transient changes in ionized calcium concentrations cause little haemodynamic disturbance and the routine use of calcium with blood transfusion is not recommended unless hepatic function is compromised. This may be caused by a low cardiac output, hypothermia, liver disease or
liver transplantation and in these situations, the chance of developing a decreased calcium concentration and citrate toxicity is increased.

Calcium also plays an essential part in both the extrinsic and intrinsic coagulation pathways. A bleeding diathesis associated with hypocalcaemia is uncommon, as cardiac arrest is said to occur before the plasma concentration decreases to a value that affects coagulation [35]. Other authors, however, have reported interference with coagulation before cardiac arrest [26].

The adverse effects of hypocalcaemia can be treated, either empirically by administration of calcium chloride if the patient becomes hypotensive and is not hypovolaemic, or on the basis of a measured decreased plasma concentration of ionized calcium [24]. Although it has been suggested that calcium gluconate is less effective than calcium chloride because it must be metabolized, this has not been proven and if equimolar quantities of each are given, no difference can be demonstrated [17]. We routinely treat hypocalcaemia with 13.4% calcium chloride containing calcium 0.912 mmol ml⁻¹ rather than the weaker 10% calcium gluconate solution which contains only 0.22 mmol ml⁻¹ of calcium.

The effects of blood transfusion on the plasma concentrations of citrate and calcium during liver transplantation have been studied [15]. During the dissection phase, plasma citrate concentration (normal range 0.08–0.12 mmol litre⁻¹) increased from the mean preoperative value of 0.09 mmol litre⁻¹ to 1.57 mmol litre⁻¹ as blood was transfused. However, during the anhepatic period when citrate metabolism did not occur, plasma citrate concentrations increased further, reaching a maximum of 3.2 mmol litre⁻¹. When the donor liver was revascularized, and metabolism of citrate was resumed, the plasma concentration decreased to 1.17 mmol litre⁻¹. Concentrations of ionized calcium decreased to 0.68 mmol litre⁻¹ (normal range 1.18–1.29 mmol litre⁻¹) as citrate concentrations increased.

**Potassium**

The potassium concentration in stored blood increases to approximately 30 mmol litre⁻¹ after 3 weeks of storage. After transfusion, viable red blood cells re-establish their tonic pumping mechanism and intracellular reuptake of potassium occurs [50]. While transient hyperkalaemia has been observed during massive transfusions and correlates strongly with the rate of transfusion [30], more commonly hypokalaemia is observed [54]. It follows that electrocardiographic monitoring is advisable during massive blood transfusions.

**Acid–base disturbances**

Three-week-old stored citrated blood contains an acid load of up to 30–40 mmol litre⁻¹ and this originates mainly from the citric acid of the anticoagulant and the lactic acid generated by red cells during storage. Both of these organic acids are normal intermediary metabolites and usually are metabolized rapidly. Citrate is metabolized to bicarbonate and may produce a profound metabolic alkalosis after transfusion. Because of this, it is not usually necessary to correct minor degrees of metabolic acidosis. The impact of transfusion of stored blood on the acid–base status of the recipient is complex, and depends upon the rate of administration, rate of citrate metabolism and the changing state of peripheral perfusion of the recipient, with shocked patients being more likely to develop a metabolic acidosis.

**OTHER COMPLICATIONS OF BLOOD TRANSFUSION**

**Hypothermia**

The problems attributable to hypothermia include reduction in citrate and lactate metabolism (thereby increasing the probability that the patient will develop hypocalcaemia and a metabolic acidosis during transfusion), an increase in the affinity of haemoglobin for oxygen, impairment of red cell deformability, platelet dysfunction and bleeding [52] and an increased tendency to cardiac arrhythmias [6]. Core temperature measurement is therefore important during massive blood transfusion and can be measured with a temperature probe at the midpoint of the oesophagus. Some workers use an oesophageal temperature probe with a stethoscope to permit monitoring of breath sounds and this is particularly useful in children. If a pulmonary artery catheter is being used, then pulmonary artery temperature can be measured in place of an oesophageal temperature probe.

Body temperature may decrease because of administration of large volumes of cold fluids and blood (which is stored at 4 °C) or because of the loss of radiant heat and latent heat of evaporation of body fluids from the open abdominal or thoracic cavity or skin (especially in burned patients). Furthermore, if ventilatory gases are not warmed adequately and humidified during operations of long duration, this contributes to heat loss; this may be prevented by the use of a heat and moisture exchanger [44].

This decrease in body temperature may be minimized by placing the patient on a heated "ripple" mattress and by warming all i.v. fluids. The patient may also be wrapped or covered in thermally insulating plastic drapes [46]. In small children an overhead infra-red heater minimizes heat loss from radiation, although this may make surgical access difficult. Alternatively, the ambient temperature of the theatre may be increased.

**Pulmonary dysfunction**

Although controversial, pulmonary dysfunction after transfusion is thought to be caused or exacerbated by the formation and subsequent administration of microaggregates formed in stored blood. The presence and composition of these microaggregates in stored blood was first reported in 1961 [49]. They are composed largely of degenerating platelets, granulocytes, denatured proteins, fibrin strands and other debris, and their rate of formation and size (10–200 μm in diameter) vary according to the different types of storage solution. Complications that have been associated with micro-
aggregate formation and subsequent transfusion include non-haemolytic febrile reactions, pulmonary injury, thrombocytopenia, fibronectin depletion and histamine release. However, because of conflicting findings in both experimental and clinical studies, controversy continues to surround the extent to which microaggregates in stored blood contribute to the production of post-transfusion pulmonary dysfunction [10]. The combination of shock, sepsis, tissue injury and massive transfusion often culminates in the adult respiratory distress syndrome.

Blood filters, designed to remove these aggregates, are of two types: depth filters which remove particles by impaction and adsorption, and screen filters which operate on a direct interception principle and have an absolute pore size rating (usually about 40 μm). A standard blood administration set contains a filter of 170 μm.

Problems which have been associated with the use of microfilters include increase in resistance to flow as the filter becomes blocked, haemolysis, platelet depletion of donor blood and complement activation. With practice, the filter usually takes less than 1 min to prime and should be changed regularly to avoid it becoming blocked. We usually change our filters after 10 u of whole blood or after about 6 u of packed red cells. Both haemolysis and platelet depletion have been attributed to depth filters only, while there is evidence that the use of screen microaggregate blood filters may actually prevent post-transfusion thrombocytopenia [29]. Significant complement activation has been demonstrated only when heparinized blood was incubated with a nylon filter [55]. Although opinions vary widely concerning the indications for use of microfilters when giving stored blood, in adults we use them when 2 litre or more of blood is to be transfused, providing they can be used without delay and do not impede the rate of transfusion.

**Increased affinity of haemoglobin for oxygen**

Valitis and Kennedy [53] were the first to observe that the oxygen dissociation curve of stored blood was shifted to the left, reaching a maximum after storage for about 1 week in acid citrate glucose. This increased affinity of haemoglobin for oxygen is caused by depletion of 2,3-diphosphoglycerate (2,3-DPG) within the red cell and may last for several hours after transfusion [1]. The depletion of red cell 2,3-DPG during storage depends upon the preservatives used and the storage time. Modern anticoagulant preservative solutions, such as citrate phosphate glucose adenine, ensure adequate concentrations of 2,3-DPG for up to 14 days after collection of blood. The clinical significance of this increased affinity of stored red blood cells for oxygen is unclear, but it may result in temporary reduction in oxygen availability at a tissue level [51]. This may be detrimental in patients with severe cerebral disease, ischaemic heart disease, anaemia or hypoxia. The adverse effects of 2,3-DPG depletion are offset to some extent by the acidosis of stored blood. As both cold and alkalosis also shift the dissociation curve to the left, it would seem prudent to give these patients warmed blood that has been stored for no longer than 7 days, and to avoid the unnecessary use of bicarbonate.

**Transfusion-transmitted diseases**

All blood products except albumin and gammaglobulin can transmit infectious diseases. Viral infections are the most commonly transmitted, with the Hepatitis C virus (causing Non-A, Non-B Hepatitis) being the most serious in terms of frequency and morbidity. Transmission of HIV by transfusion has been extremely rare since the introduction of HIV antibody screening in 1985.

**CASE REPORT**

Although the adverse effects of a massive blood transfusion are well described in all of the major text books, in the authors' experience they are uncommon. We report a patient whose case illustrates the syndrome well (table V), although it should be emphasized that the patient concerned offered an extreme example of the difficulties.

The patient was an 8-month-old, female child presenting for liver transplantation because of end-stage liver disease resulting from biliary atresia. This had been treated previously at the age of 6 weeks by portoenterostomy (Kasai procedure). Unfortunately, this was unsuccessful and because of the infant's increasing disability and failure to thrive, orthotopic liver transplantation was considered necessary. The operation was technically difficult because of the previous surgery and the profound preoperative coagulation disturbances. The estimated blood volume in this child was 0.53 litre (a significant amount of ascites was present, artificially increasing the body weight).

From the start of the operation to the period when the vascular clamps were applied, approximately 10 blood volumes were lost. This was replaced with banked blood in excess of 72 h old because the patient had anti-E antibodies and fresh blood was not available. The ionized calcium decreased from 1.1 to 0.79 mmol litre⁻¹, despite the administration of calcium chloride 50 mmol. The plasma potassium concentration increased from 4.2 to 7.5 mmol litre⁻¹.
MASSIVE BLOOD TRANSFUSION

Because of concern that a further increase in potassium might occur when the liver was revascularized, prompt treatment was considered necessary, therefore 50 % glucose 10 ml and insulin 2 u were administered. In addition, a large dose of frusemide (10 mg) was given. A further dose of glucose and insulin (50 % of the previous dose) was administered 5 min before revascularization. The urinary potassium concentration did not increase (119 mmol litre\(^{-1}\)) and the excretion of potassium. This, together with the administration of glucose and insulin, decreased the plasma potassium concentration to a value whereby revascularization proceeded uneventfully. In the event, there was a degree of overshoot necessitating the administration of potassium chloride during operation.

Despite efficient blood-warming and pyrexia before operation, the nasopharyngeal temperature decreased steadily and a further decrease was seen when the donor liver was revascularized (having been stored at 4 °C). After revascularization, the temperature did not decrease further.

Plasma sodium concentration increased throughout the procedure, from 130 mmol litre\(^{-1}\) at the beginning to 154 mmol litre\(^{-1}\) at the end; this reflects the sodium contained both in blood and blood products. Activated clotting time was maintained at almost 10 circulating blood volumes. All blood was filtered through a 40-μm filter and acute lung injury did not develop in this patient, despite the transfusion of almost 10 circulating blood volumes.

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We thank Dr J. R. Klinc and Mr M. F. Smith for their helpful advice in the preparation of this article.

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12. Ganymes G. insulin (50 % of the previous dose) was administered 5 min before revascularization. The urinary potassium concentration did not increase (119 mmol litre\(^{-1}\)) and the excretion of potassium. This, together with the administration of glucose and insulin, decreased the plasma potassium concentration to a value whereby revascularization proceeded uneventfully. In the event, there was a degree of overshoot necessitating the administration of potassium chloride during operation.

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