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# RATIONAL USE OF BLOOD AND BLOOD PRODUCTS

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## INTRODUCTION

During tlie Spring of 1987 the author had the privilege of visiting the Pathology Department of the University of Malaya in Kuala Lumpur and was able to witness many aspects of local clinical practice involving blood therapy including heart surgery and bone marrow transplantation. It is acknowledged that the demographic situation in Malaysia differs considerably from that in Scotland; nevertheless, there are principles which are common to all countries when it comes to the rational use of blood.

## VIRTUES OF BLOOD

It seems obvious that human blood represents the "ideal" in replacing acute blood loss. Although this may appear to be self-evident, in that both plasma protein and haemoglobin are replaced, it is actually the red cells and their oxygen carrying capacity which reverse the hypovolaemic shock. Hence it is generally recognised that it is highly desirable to maintain the haematocrit above 10% in persons who are bleeding rapidly. The possible role of "fresh" blood, and of fresh plasma and platelets in the support of the massively bleeding patient will be discussed later.

## HARMFUL EFFECTS

Blood transfusions may do harm by provoking an immediate and sometimes fatal haemolytic transfusion reaction – usually due to ABO incompatibility.[1] Other less dramatic hypersensitivity phenomena may result from the presence of other red cell antibodies in the patient and of factors such as kininogen breakdown products.[2] Delayed hypersensitivity, whereby transfused red cells may be destroyed by an anamnestic response to a specific antibody several days after the transfusion are well described[3] and can embarrass renal function. Such immunological phenomena may have adverse effects on further pregnancies.

Acute febrile reactions are not uncommon with blood transfusions, particularly to multiparous women or men who have had previous transfusions. These are usually due to the patient having antibodies to transfused white cells, platelets or plasma protein.[4]

Stored blood undergoes changes that may have adverse effects on the patient, such as the fall in red cell 23 DPG (producing increased oxygen avidity), a rise in plasma potassium (up to 30 mEq by outdate) and the development of microaggregates from white cell and platelet debris.

Blood can also transmit infections, either through colonisation of the donation by external micro-organisms – usually bacteria;[5] or by transmitting infections, usually viral, from the asymptomatic donor.[6]

## PRINCIPLES OF BLOOD BANKING

The first blood bank was set up 50 years ago in Cook County Hospital, Chicago.[7] This was based on the principle of deposits by friends and relatives of patients linked to withdrawals for patients at need. For a short time there was apparently a series of cash transactions. Hence the hospital had a "bank" in the literal sense of the word. Since then, the term blood bank has become less specific and indeed might now be regarded as outmoded particularly in the West.

The storage of blood requires specific facilities and one obvious principle is that in order to avoid excess outdating, blood which has been stored the longest should be used first.

## PRINCIPLES OF "SELF-SUFFICIENCY"

The WHO has endorsed the principle whereby individual nations develop a state of "self-sufficiency" with regard to the supply of blood and blood products.[8] This means that within the resource of the community blood should be donated within the health service structure and made available for patient use. In these days of sophisticated blood products fractionated from donated plasma and cells, the principle of self-sufficiency should extend to all blood products.

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The process of preparing components from blood is relatively simple (platelet concentrates, plasma, cryoprecipitate) but the system of plasma fractionation requires a pharmaceutical grade "factory" with approved facilities for the production of safe pharmaceutical grade materials.

There are few countries that have achieved true self-sufficiency. The United States has been described as the "OPEC" of the plasma fractionation industry but certainly in the past some of the plasma obtained for fractionation has come from outside the United States.

It seems to be the smaller countries of Northern Europe such as Scotland, The Netherlands, and the Scandinavian countries which have become most successful in true "self sufficiency" as have also France, Switzerland, Australia and New Zealand. England still imports considerable quantities of clotting factors from commercial companies and the same goes for many emerging nations who have been able to develop a reasonably high standard of medical care for certain sectors of the population but have no fractionation facilities.

It has been calculated that in order to sustain self-sufficiency of red cell products, a donation rate of 40,000 per million should be collected. However, this is not sufficient for plasma self-sufficiency which may require a figure of nearly double this quantity. The imbalance between plasma and red cell requirements may be met either by deliberate "over bleeding" with the possible result of excessive red cell discarding, or by developing a system of regular donor plasmapheresis.

The question of donor remuneration is important. Many surveys have demonstrated that the quality of plasma from paid donors is generally inferior to that from volunteer healthy donors.' Although the worst excesses of the past may now be less common, there have been well established examples of deprived persons selling their blood and obtaining a considerable proportion of their family income from such sales. Such persons are more likely to be at risk from parasitic diseases and hepatitis, and in those parts of the world at risk also from HIV infection. It is noteworthy that by the early 1980's the American red cell donation base had become almost completely volunteer, although the plasma fractionation industry still obtained virtually all its plasma through commercial origins.[9]

## BLOOD AND ITS PRODUCTS

### Whole Blood Donation

In Britain it is usual for 450 mls of blood to be collected into 63 ml of anticoagulant (usually "CPDAI"). Donors have to be at least 8.5 stone (55 Kg); there is no provision for healthy donors under this weight although in parts of the world where persons of slighter stature are more common it is perfectly feasible to collect, say, 300 mls of blood into 42 mls of CPDA1. The lowest haemoglobin level accepted is 12.5 g/dl for women and 13.5 g/dl for men. Healthy donors between the ages of 18 and 65 are accepted.

Donors may be bled within 5 minutes without untoward effect, although it is advisable for them to remain resting in the recumbent position for at least 10 minutes after donation. Replacement with oral fluids (in Britain a cup of-tea) is advisable and most donors may leave after 30 minutes. The blood volume deficit is recovered within this time from the extravascular fluid but the 200 mls or so of red cells (equivalent to about 240 mg of iron) will take a few weeks to recover, to some extent dependent upon the donor's iron stores. Although it is not usual practice in Britain to supply iron supplements, there is no reason why this should not be done if donors, particularly women, are on the verge of iron deficiency. In Britain male donors may donate up to three times a year, although in other parts of the world donations of up to every two months have been approved.

### Effects of Storage

Whole blood in CPDAl may be stored at 4°C for up to 5 weeks.[10] The storage conditions need to be extremely well controlled and monitored constantly. Provision of emergency power supplies is necessary to protect the blood from electricity cuts. Five weeks storage has been shown to retain viability of at least 75% of the red cells, as shown by recovery in the circulation 24 hours after transfusion. Granulocytes and platelets become non-viable after 24 to 48 hours at 4°C and the more labile clotting facotrs (particularly V and VIII) decline more rapidly on storage (although less rapidly than commonly supposed).

Red cell 23DPG remain stable in CPDAl for about 7 days but thereafter declines rapidly to become undetectable by 15 days. This is accompanied by a shift of the oxygen affinity

curve to a P50 of about 22 ml Hg (normal 27 mm Hg). The clinical relevance of this is unclear; it is therefore unlikely to be of great significance.[11] Red cell membranes become more rigid during storage and plasma potassium levels rise up towards 30 mEq by the expiry date. Effete white cells and platelets and fibrin strands accumulate after about 7 days to form microaggregates which become progressively more noticeable throughout storage.

These changes are accelerated if blood spends significant periods at temperatures above 4°C. For example withdrawal from a refrigerator into room temperature (20°C) for 30 minutes may be accompanied by a temperature rise of the pack to 6 or 8°C; red cell catabolism may thereby be doubled, accelerating the changes described.

Blood Products – Red Cells and Platelet Concentrates

Unmodified whole blood is now not usually found in Scottish blood banks. Donations taken into primary packs with satellite secondary and tertiary packs attached allow sterile separation of important blood components. The drive for plasma products, particularly albumin and factor VIII, have lead to a preponderance of red cell concentrates from which more than 200 mls of plasma have been withdrawn. Alternatively, or in addition, platelets may have been withdrawn from the pack, to be concentrated in 60 mls of plasma in a satellite pack. Each platelet concentrate thus obtained usually contains between 60 and 90% of the originally donated platelets.

Optimal additive solutions enable more plasma to be extracted from each whole blood donation." These solutions consist of a nutrient mixture with saline and glucose and additional compounds such as adenine, citrate, mannitol, sorbitol etc. Various formulations have been developed by commercial companies, the most common being mixtures of saline, adenine, glucose and mannitol marketed by Fenwal in 2 forms – SAGM, or ADSOL. The volume of such solutions is usually 100 mls. Shortly after donation, the unit is centrifuged hard and all plasma taken off. The red cells are then suspended in the optimal additive, thus achieving a haematocrit of about 60% and good flow properties. The shelf life may be 5, 6 or even 7 weeks, but the changes in the suspension alluded to above are still operative, including the development of microaggregates which may, in the absence of citrate, actually form a solid gel-like lump.'[13] This is apparently harmless.

**Plasma and** Cryoprecipitate

This plasma obtained, either in the optimal additive system or from the straightfoward red cell concentrate preparation, may be frozen within hours of collection and forms the basis of clinical "fresh frozen plasma". Cryoprecipitate can be manufactured from this product by allowing careful thawing at 4°C, which leaves behind a gel-like precipitate material, and removing the supernatant plasma. The cryoprecipitate remaining can be refrozen and is a useful source of plasma enriched in fibrinogen and factor VIII.[14]

All these processes are feasible within a standard blood collection and blood banking centre. Good freezing facilities are required and the best freezing is achieved using either liquid nitrogen or a suspension of carbon dioxide snow in alcohol. However, reasonable quality fresh frozen plasma and cryoprecipitate may be made by using more conventional deep freezers with operating temperatures of −30 to −40°C. Good centrifuge facilities are also, of course, essential for getting good quality plasma depleted of most of the platelets, or alternatively when required platelet rich plasma for the preparation of platelet concentrates.

Fractionation Products

Plasma fractionation requires sophisticated pharmaceutical quality facilities. The Cohn fractionation principle is still widely applied; this uses cold ethanol and various pH adjustments to acid states. The products prepared, which include albumin solutions, freeze dried preparations of factor VIII and factor IX concentrates, liquid preparations of immunoglobulins for intramuscular use or freeze dried preparations of irnmunoglobulins for intravenous use, are produced by the Scottish National Blood Transfusion Service (SNBTS) at a specially commissioned fractionation centre in Edinburgh. All these products can be submitted to viricidal procedures and although the most challenging viruses remain those that cause non A non B hepatitis, there are reasonable grounds for assuming that HIV can be eliminated from these products by proper and well conducted procedures. The details of such procedures vary, being described variably as "wet heat", "steam heated", or "dry heated". There is some evidence that the wet heating

process may be more effective than some of the shorter drier heating processes,[15] but the dry heating process used within the SNBTS requires 80°C at 72 hours and is highly viricidal ***ex-vivo.***[16] Care has to be exercised in assessing the claims of manufacturers. For example, one manufacturer has claimed that their process of viral inactivation is by wet-heating when in fact the blood product is merely immersed in an organic solvent which does not "wet" the products. Critical judgements require a degree of expert knowledge; but the crucial ***ex-vivo*** assessment is the "log-kill" rate of established hardy viruses when materials are deliberately contaminated. Suitable viral markers are Rous Sarcoma Virus, or Feline Leukaemia Virus if working conditions for handling HIV are not available.[16]

In order to prevent the blood product becoming denatured, protective systems which often use saccharides (maltose, sucrose or sorbitol) are necessary. It may also be assumed that to some extent the virus may be similarly protected from destruction. Ultimately the results will depend upon monitoring of the materials in clinical use although some information may be obtained by ***ex-vivo*** testing on cell cultures. ***In vivo*** testing in the rather precious chimpanzees can be useful but only to a limited extent as even the chimpanzee may not react in exactly the same way as Homo Sapiens. Indeed, products which have failed to transmit hepatitis to chimpanzees have done so to man.

## PRE-TRANSFUSION COMPATIBILITY TESTING

Because of the understandable desire to avoid transfusing blood which is potentially incompatible, much emphasis was made until the late 1970's on increasingly refined and exhaustive tests. These were designed to see if there were any antibodies in the patient's serum that are capable of reacting ***in vivo*** with cells supplied in the donation. Various techniques and temperature ranges became commonplace.'[7]

This approach is limited; firstly the quality of the donated cells may be variable and significant clinical reactions missed by the preliminary ***in vivo*** tests; on the other hand the plethora of techniques often generated delay in the issue of blood while unexpected reactions were investigated further. The current approach in the United Kingdom is to apply tests that are most likely to detect clinically significant antibodies." All tests are conducted at 37°C and only two techniques are recommended; the antiglobulin test (Coombs' test) is mandatory and some other form of testing, usually on enzyme treated cells or tests involving albumin replacement techniques. Furthermore, greater sensitivity can be achieved by the selection of optimal quality red cells of detailed known antigenic composition selected from stocks. Alternatively such cells may be obtained commercially. The current trend is to use 3 cells which, because of the frequency of Rh negative individuals in Europe (15 to 17%) gives much emphasis to the Rh D state (Table 1). In communities where the D antigen is much less common, alternative designs may be more suitable.

## THE "MAXIMUM SURGICAL BLOOD ORDERING SCHEDULE" (MSBOS)

These techniques have allowed the development of the "group and screen" techniques, whereby patients' blood can he grouped and the serum tested for the presence of atypical but potentially clinically significant antibodies. This in turn has lead to the development of a more logical system of using blood in an effort to conserve the bank stocks. For example surgical procedures which only rarely require blood to be transfused (such as cholecystectomy) may be conducted without blood being sent up to the operating theatre from the blood bank so long as the blood bank is capable of supplying blood of the appropriate group should there be complications during surgery. Alternatively, if the patient's serum can be demonstrated to contain antibodies of known specificity, blood negative for the relevant antigens may be selected in advance.

The beneficial effects of these is to remove excessive blood from the "bespoken" category for specific patient use. This will increase the stocks of uncrossmatched blood making them more available should the need arise.

Along witn this technical advance is developed the need for greater surgical clinical consideration such as the development of the "maximum surgical blood ordering schedule".'[9] According to this schedule, certain operations when conducted electively on certain patients may generate automatically a response from the blood bank depending upon previous experience. Hence a group and screen only may be conducted or the issue of two, four or more units of blood. An efficient MSBOS should lead to less than two units of blood being crossmatched for every one transfused.

**TABLE 1**
**ANTIGENIC "SPREAD" OF A TRIPLE PANEL OF RED CELLS USED FOR SCREENING PATIENT SERA SUBMITTED TO THE BLOOD BANK OF THE ROYAL INFIRMARY OF EDINBURGH**

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| **Positive Control** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Negative Control** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Reference** | **Pack No.** | Gp. | Pheno | DCT | | Cw | D | Du | **E** | c | e | **M** | N | S | s | P | Lua | Lub | K | **k** | Kpa | Kpb | Lea | Leb | Fya | Fyb | Jka | Jkb | $Wr^a$ | |
| T01 | LPY | O | $R_1^w R_1$ | – | + | + | + | | – | – | + | + | + | + | – | + | – | | – | + | – | | + | – | – | + | + | + | – | |
| T02 | NCN | O | $R_2 R_2$ | – | – | – | + | | + | + | – | – | + | | + | – | – | | | + | + | | + | – | + | + | + | – | – | |
| T03 | RMM | O | rr | – | – | – | – | | – | + | + | – | + | – | + | ++ | – | | + | + | – | | – | + | + | – | – | + | – | |
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Note the presence of the Kell antigen on the Rh negative cells (cell T03), the $C^w$ antigen on cell T01; and the presumed homozygous expression of Fya, Fyb, Jka and Jkb on certain cells which offers optimal detection of weak antibodies. These cells were all obtained from blood donors presenting to the S.E. Scotland BTS in Edinburgh.

## MANAGEMENT OF ACUTE BLOOD LOSS

Massive bleeding may be defined as the loss of more than one whole body blood volume of blood over 24 hours or less; or of half the blood volume in 4 hours or less. The clinical management will depend upon whether the patient was previously healthy (for example a young person sustaining multiple trauma, or a young woman with a sudden obstetric complication) or whether the patient is an older frailer person undergoing major elective surgery.

A steady fast loss may cause no particular problem if blood replacement keeps up. However, trauma patients in this situation frequently undergo periods of profound hypovolaemia followed occasionally by hypervolaemia as the medical attendants desperately try to compensate for the blood loss. The steady replacement of one whole blood volume (about 5 litres for a 70 Kg man) will result in the platelet count dropping to about one third of the starting level[20] but this may well still be enough to achieve good haemostasis once the source of the blood loss is controlled. Similarly, there may be no evidence of consumption of clotting factors.

Nevertheless, where the clinical status may fluctuate widely, evidence of defibrination and platelet consumption may follow and be documented by basic coagulation screens. Ideally these should consist of a prothrombin time ratio, a PTT, fibrinogen level and platelet counts at the very least.[21]

The choice of volume replacement is important. So long as there is no renal impairment, a massive infusion of saline can be very effective in restoring the patient's volume and vital signs.[22] However it is important to avoid the haematocrit dropping below 10%[23] and an infusion of red cells will be necessary in the event of continued rapid blood loss. If vigorous total volume replacement is still being pursued, it may be wise not to commence the blood infusion as whole blood but rather as red cell concentrates. However, if there is a documented depletion of clotting factors and/or platelets, the relevant blood product (FFP, platelet concentrates) may be indicated. Proponents of colloidal solutions as volume expanders argue that these help maintain oncotic intravascular pressure. However, this may be invalidated by the capillary leak that accompanies shock. Hence the widespread use of pla'sma protein solutions as volume replacement for acute bleeding is to be discouraged (quite apart from its expense). Even the artificial (and cheaper) colloids such as the gelatins ("Gelofusin", Haemaccel") or the dextrans (including hydroxy-ethyl starch) have only a limited place. Plasma protein solution, or physiological albumin solutions are most useful in renal dialysis, plasma exchange and judiciously in intensive care units for the long term gravely ill patient with fluid retention problems.

Fresh frozen plasma has also been advocated on the assumption that it is able to replace the more labile clotting factors. However there is evidence of gross overuse in the United States of America,[24] and it is recommended that its use in the management of massive bleeding be restricted to the occasions when a consumptive coagulopathy has been clearly demonstrated (by laboratory tests).[21,25] Defibrination may require cryoprecipitate therapy.

In Britain, there is no place for the use of fresh blood as all the haemostatis characteristics which can be ascribed to fresh blood may be available from platelet concentrates. Occasional requests are still made, but have no foundation in practice. However, it is appreciated that in countries with a less established tradition of blood banking it may be necessary to obtain a source of blood replacement rapidly. If the source can be obtained from accredited donors (i.e. those who are virologically safe) it may well be possible to transfuse such patients with blood less than 12 hours old and which will contain the vital haemostatis characteristics required. However, reliance on such a system is highly unsatisfactory, and a well stocked and supported blood bank with all blood products from red cell concentrates to plasma concentrates is highly desirable.

## SELF SUFFICIENCY, PLASMA FRACTIONATION AND GENETICALLY-ENGINEERED "PRODUCTS"

Plasma fractionation for pharmaceutical purposes is an expensive process – the British Government have invested tens of millions of pounds sterling in their Blood Products Laboratory in order to achieve complete self sufficiency in England. Some genetically-engineered products are reported as being at an advanced stage of development, particularly clotting factor VIII and albumin. It is assumed that these will be free of the risk of viral transmission. Is it therefore worthwhile for emerging nations to invest in such developments, or should they be resigned to obtaining such products from the Western-dominated

international commercial companies?

The need for fractionation products from high quality donated plasma is likely to be with us until the end of the century, at least for many products. Immunoglobulins for intramuscular and intravenous use for "non-specific" protection cannot be provided by mixtures of monoclonal antibodies even if the barrier to mass-production of human immuno-globulins ***in vitro*** is breached. Purer preparation of clotting factor VIII may be produced from donor plasma if processed through monoclonal antibody absorption columns; and considerable developmental problems still face the marketing of genetically engineered factor VIII. "Minor products" such as Willebrand factor, alpha-l-antitrypsin, antithrombin III, Protein C, caeruloplasmin, fibronectin etc, produced by genetic engineering, will take many more years to become a viable commerceial option. Furthermore, the viral safety of products from "large pool" human donations is considerably enhanced by refined Pasteurisation techniques.

However, how can small countries like Malaysia develop such a facility within their own health structure? It would be arrogant of this author to make specific suggestions, but it may well be that such projects need Regional International Cooperation. The advantages would be that not only would such Regions become independent of extra-Regional market forces, but that self-sufficiency would extend to the processing of reagent production and quality assurance schemes so essential to a healthy national Blood Transfusion Service.

## FINAL COMMENT

Finally, the author would like to comment that the United States and Europe have seen the emergence of a new discipline – "Transfusion Medicine".[7] This is a clinical discipline, founded firmly in clinical pathology involving the procurement of blood and related products right through to the safe, effective and optimal infusion of those products. The discipline is closely related to haematology in many aspects but also shares much in common with immunology, microbiology and clinical chemistry, as well as the clinical disciplines of anaesthesiology, surgery and obstetrics. Along with national self sufficiency, the development of specialists in Transfusion Medicine – whose professional input must be allowed to develop along rewarding clinical pathways as well as developing responsibility for the establishment and supervision of blood banking – seems very opportune.

The author understands that cultural traditions may hinder the willingness of certain societies to support a system of voluntary blood donations given willingly, frequently and anonymously. However, certain advances in medicine continue to rely heavily on human blood and its products. Not only in such high technology fields as heart surgery and leukaemia therapy, but also as replacement therapy in thalassaemia, the haemophilias, and for the support of traumatised children and adults. I feel strongly that in those emerging societies where the concept of free and willing blood ddnation is still to be adopted widely, there is an obligation on the well-educated, including doctors and nurses, to give a lead, not only by donating blood regularly but also by supporting the establishment of a system of detailed organisation such a programme requires.

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