Spring 2011 • Issue 33

NHS Blood and Transplant

# Blood and Transplant Matters

Information for hospitals served by NHS Blood and Transplant

## Inside



# EDITORIAL

Once again it is a pleasure to introduce this issue of *Blood and Transplant Matters* which features a wide range of articles on clinical transfusion including: cell salvage, bacterial screening of platelet concentrates, transfusion-related acute lung injury, monitoring of infectious agents, major haemorrhage in trauma patients and alloimmunisation in pregnancy. As always, the Editorial Board is delighted that we have managed to persuade so many illustrious individuals to write for your benefit. I will not list them here or try to summarise in a few words the thrust of their articles; you will find out for yourself as you flick through the next thirty or so pages. For some time *Blood and Transplant Matters* has tried to reflect the huge developments in tissue, stem cell and organ transplantation in its contents and this issue is no exception with scholarly contributions on knee surgery, vigilance and surveillance of substances of human origin, the ethics of bodily donation and regenerative medicine.

In recent years we have developed some new themes – 'A Day in the Life Of', Famous Lives (past and present) and Transfusion in Developing Countries. In this issue you will find an account of the lives of Robert Race and Ruth Sanger, so hugely influential in understanding human blood groups, and Bernard Loty a pioneer in cell and tissue banking. Following on from our two part 'Immunology for Dummies' we have persuaded Sarah Alford to write the first of two parts of what I originally planned to call 'Clotting for Idiots' – now Coagulation Update: Part 1 (I decided to avoid insulting the intelligence of readers of *Blood and Transplant Matters!*). Finally, Biddy Ridler describes her adventures with the Higher Education Academy.

I hope that you will find this a balanced selection and would like to welcome two new Editorial Board members Dr Paul Rooney and Professor James Neuberger who will help to ensure that the interests of tissues and organ donation and transplantation continue to receive a high profile. I am grateful to Ruth Warwick and Clare Taylor whose contributions will be missed.

Those who write for us aim to synthesize current knowledge and conjecture and provide clarity and understanding across a broad readership. I am convinced that they do a great job and hope that you will agree, although it is impossible in my view to make everything totally accessible without dumbing down too much. As Henri Poincaré, writing in *Science and Hypothesis* (1905) stated: 'Science is built up of facts, as a house is built of stones; but an accumulation of facts is no more a science than a heap of stones is a house'. I hope that you will admire the construction of the science assembled in this issue and would also be delighted to hear any comments that you have for improvements or for future articles.

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# A Cell Salvage Update

It is ironic that advances in blood transfusion have been driven by crises; often related to conflict, epidemic or finance. The current era of blood conservation sits well alongside global themes of conservation and re-cycling. Intraoperative cell salvage (ICS) is a prime example.

ICS was originally a by-product of the centrifugal blood separation device designed by Jack Latham. The Latham bowl was introduced to separate plasma from red cells during the Vietnam war. In the 1960's the impetus was financial. A rapid rise in the numbers of coronary bypass operations led to a drain on blood stocks, because surgeons transfused liberally, often up to 12 units per case.

In the 1980's the emergence of HIV and the hepatitis scandals led to a new interest in reducing donor exposure. The available techniques were re-evaluated and some surprising results emerged. Isovolaemic haemodilution was ineffective unless taken to extremes. Predonation led to anaemic patients who needed red cells earlier in the operation. Directed donation led to ethical worries about pressurising relatives who might have confidential reasons not to have their blood tested. Cancellation of surgery led to blood wastage. Promising drugs such as aprotinin proved to be unsafe.

Blood conservation now centres on optimising patients before surgery to create a reserve in blood volume, techniques to reduce bleeding such as the withdrawal of anticoagulants, careful surgery and tolerance of lower post-operative haemoglobin.

In autologous blood transfusion, ICS has been the sole survivor. The main reasons are:

- A good safety record
- Cost effective at only two units re-cycled
- A safety net for unexpected bleeding
- Indications are broadening.

The rapid adoption of ICS has happened despite a relative paucity of level 1 evidence regarding its efficacy. This is probably pragmatic. It just works, so it has been introduced in much the same way as laparoscopic cholecystectomy, without the need for trials. In the future, the benefits in avoiding blood transfusion make a randomised trial increasingly unlikely for ethical reasons.

Advances in ICS include new indications such as cancer surgery, general surgery and trauma. The UK Cell Salvage Action Group has championed ICS training; quality control is emerging and adverse event reporting has been introduced. Managers are being convinced of the sound economic sense of ICS.

## *ICS and Malignancy*

In the early 90's, the risk/benefit ratio for transfusion in cancer surgery seemed poor. Third party transfusion was associated with increased risk of peri-operative infection and cancer recurrence due to immune modulation. There were no studies showing dissemination of cancer cells during ICS at the time. We were discussing ICS with all our patients and recording their consent in the notes. With the agreement of our urology colleagues we introduced ICS into major bladder, prostate and kidney resections. Despite using no ultra filtration before reinfusion there were no cases of blood-borne metastasis. Our experience is now approaching 1,000 patients and has been paralleled by the Morriston Hospital team, who have been using leucodepletion filters.

Urology is a good example of the continued relevance of ICS. Despite the use of every adjunct available to minimise transfusion and the emergence of a new breed of surgeon who is careful to control bleeding, ICS provides a safety net in cases of unexpected blood loss such as advanced cancers or anatomical variants, especially venous.

ICS has been approved by NICE for use in urological malignancy and is now the biggest user of ICS in our centre. Please see http://www.nice.org.uk/IPG258

## *Obstetrics and Gynaecology*

Amniotic fluid embolism (AFE) is a rare (1 in 20,000 deliveries) serious condition leading to maternal death. There were naturally great concerns regarding reinfusion of the components of amniotic fluid by ICS, but over the last ten years these concerns have been overcome. It has been appreciated that amniotic fluid can be found in the maternal circulation during normal delivery, when the intrauterine pressure rises above central venous pressure. Amniotic fluid embolism is in fact a complex combination of hypotension, shock and coagulopathy similar to so-called fat embolism syndrome.

Pioneers of the use of cell savage in obstetrics, notably Sue Catling and her team in Swansea have adopted a similar pragmatic approach, by carefully auditing cases and looking for complications. The risk of maternal death due to bleeding will always be greater than the risk of AFE especially in high risk cases such as placenta accreta or praevia and to date there have been no adverse events associated with the use of ICS in obstetrics. One sensible precaution is to use a double suction system. A waste sucker is used first to evacuate the uterus, followed by the ICS suction.

NICE guidelines have also been released – at http://www.nice.org.uk/guidance/IPG144

Few gynaecologists use ICS in malignancy, but there is no reason to suppose that it will be unsafe, based on the urology experience.

## Orthopaedics and Trauma

The use of ICS is now well established in orthopaedics. The only real area of concern is in revision surgery for sepsis, which is clearly unwise. Paediatric cases, especially scoliosis surgery, are very important indications because young patients have a long life expectancy and are vulnerable to slow viruses and other potential infectious complications of bank blood.

Trauma is another area to consider the use of ICS. There are few concerns regarding infection in the era of careful fluid resuscitation and broad-spectrum antibiotics.

## General Surgery

We originally introduced ICS for Jehovah's Witnesses undergoing colorectal surgery after hearing of the Eindhoven experience from Peter Everts. Similar arguments exist regarding malignancy and sepsis, but our colleagues are increasing the numbers of cases where ICS is used, especially in pelvic surgery. Splenectomy, gastric and pancreatic resections are also suitable.

## Cardiothoracic Surgery

Cardiac surgery is a good example of a speciality that has taken blood conservation seriously. Surgical advances such as off-pump bypass and minimal access techniques have reduced transfusion to near zero in leading centres and comparative audit has encouraged units to compete with their peers. Use of haemostatic agents and adjuncts such as tranexamic acid have become routine. Nonetheless, valve replacement and aortic arch reconstruction are perfect indications for efficient use of ICS.

In thoracic surgery, oesophageal and lung resection may be good indications for ICS, but improved techniques such as minimally invasive surgery are reducing transfusion requirements.

## Vascular Surgery

Aortic surgery was once the main user of ICS in most hospitals, but no more. About 70% of aneurysms are suitable for endovascular repair (EVAR), which has been a major advance, with no transfusion, shorter stay and no requirement for ITU. Screening for aneurysms is being rolled out nationally for 65 year old men and it is hoped that there will be an incremental fall in surgery for rupture.

A recent audit in our unit has revealed a survival advantage in those with ruptured aortic aneurysms who had ICS. Vascular surgeons did all the procedures. In operated patients the 30-day mortality was 26% in those who did not have salvage, but only 13% in those who did. There are likely to be confounding variables such as ICS being requested by "vascular" anaesthetists and ICS being less likely to be available at night, but the magnitude of the survival advantage is compelling. So is the large cost saving in terms of donated blood, blood products and expensive drugs.

## Increasing the Efficiency of Cell Salvage

The provision of a reliable ICS service, a group and screen and rapid provision of blood from the transfusion laboratory has meant that for the last 15 years we have not cross-matched blood at all for aortic surgery. The "Agreed" surgical blood ordering schedule (ASBOS) is revised annually with individual teams so that we are almost a "zero cross-match" hospital. The few exceptions include scoliosis surgery in <20Kg patients, liver resection and those patients who require irradiated blood.

Disposable use is minimised by opening only the collection reservoir at the beginning of cases. If enough blood is salvaged to process, the centrifuge set is opened. Low volumes of blood are processed at the end of a procedure on the basis of near patient testing. If the administration of ICS blood is likely to bring the haemoglobin level above the agreed trigger, it is worthwhile processing volumes that might be considered marginal. Communication is central.

## Training, Quality and Implementation

The UK Cell Salvage Action Group (CSAG), working alongside the NHSBT Appropriate Use of Blood Group, has worked very hard developing tools to help hospitals set up an ICS service, to train operators, answer queries and educate patients. The UK Blood Transfusion and Tissue Transplantation website http://www.transfusionguidelines.org.uk provides a useful one-stop resource.

Recent developments in ICS include the introduction of microbiological and washout efficiency quality control indicators. SHOT has teamed up with the CSAG to record adverse events such as procedures abandoned due to operator or equipment failure and adverse clinical events.

All hospitals should have a clinician with overall responsibility for ICS but it is also necessary to have help on the ground. We have employed an Operating Department Practitioner (ODP) with specific responsibility for training and making sure that trained operators keep up their numbers. She helps with audit and research and

works with consultants' secretaries supporting machine bookings. One invaluable resource has been an ICS booking diary, which is held in a "public" Microsoft Outlook folder on the Trust's intranet.

We envisage ICS becoming a core competency of ODP training in the future. In our view an ICS machine is a standard item of theatre equipment like an anaesthetic machine and the principles of operation are generic. It is also a useful skill for trainee anaesthetists to acquire.

### *Conclusion*

ICS is an indispensable piece of equipment that should be available in all operating theatres. The many advantages are manifest to all involved – the surgeon, anaesthetist, transfusion service and finance director, but most importantly, our patients.

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## Bacterial Screening of Platelets

Bacterial contamination of platelet components is a serious, potentially life threatening, hazard of transfusion. Since the inception of SHOT in 1996 (the UK Serious Hazards of Transfusion Haemovigilance Scheme), and including data for 2009, there have been 33 incidents confirmed, of which eight were fatal. This is considered to be an underestimate of the true picture as there is likely to be under-recognition and reporting. This is the most common transfusion transmitted infection.

In 2005 NHSBT (and all UK Blood Services) introduced a number of safety measures to reduce bacterial contamination in platelets. These include:

1. Use of diversion pouches – the first 20 to 30ml of blood is diverted into a sample pouch rather than the main pack. The rationale behind this is that any bacteria which may enter the collection system from the skin plug during venepuncture would then be diverted away from the main pack and would not contaminate the final component.
2. Improved arm cleansing – there are incontrovertible data demonstrating the superiority of 70% isopropyl alcohol with 2% Chlorhexidine Gluconate as the most effective method for arm cleansing prior to venepuncture. This method has now been implemented in all UK Blood Services.

Recent analysis has shown the risk of bacterial contamination fell by at least 80% as a result of introducing procedures to reduce contamination from the donor skin at the time of venepuncture. The measures introduced were aimed at minimising the risk from this route.

Infections due to bacterial contamination continue to occur. Since 2005, a further nine cases have been reported in England, with three deaths. With the increase in proportion of platelets obtained by apheresis, each infected platelet collection has the potential to infect two or even three patients; this was seen twice during 2008 and once again in 2009.

The NHSBT Board agreed in January that we should implement Bacterial Screening as soon as possible for the following reasons:

- Patient safety is a prime consideration
- The risk of bacterial contamination can be further reduced by implementing screening
- Bacterial screening is in place in the three other UK Blood Services
- The high use of apheresis platelets increases the risk of infecting multiple patients
- The costs are not out of line with other measures to prevent transfusion fatalities.

Work on detailed planning for the implementation started last year. Implementation is planned to be completed by the middle of 2011. This reflects the complexity of the process, changes to NHSBT computer systems, space development as appropriate, implementation and training of staff. The first site to go live will be Manchester in late February 2011.

If you have any questions, please contact Ian Reeves on 01223 588 712 or e-mail ian.reeves@nhsbt.nhs.uk

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http://www.shotuk.org/home/

# Transfusion Related Acute Lung Injury: A New Perspective for an Ongoing Problem

Transfusion Related Acute Lung Injury (TRALI) was coined by investigators from The Mayo Clinic in 1985. The pathogenesis of TRALI was originally thought to be due to the infusion of donor antibodies into a recipient that expressed the cognate antigen on their leukocytes, especially neutrophils (PMNs). These donor antibodies then induce PMN sequestration and activation resulting in endothelial cell injury, capillary leak and acute lung injury (ALI). The incidence of transfusion continues to rise partially due to an aging patient population with advanced surgical and oncological procedures that require transfusion. Importantly, donor antibodies infused into a recipient that expresses the cognate antigen are not enough to cause TRALI as determined in multiple donor look-back studies of the minority of patients that express the cognate antigen who do not develop TRALI when infused with donor plasma which contains the specific antibodies.

TRALI has been vastly under-reported, with 8-21 cases reported annually from 1998-2003 despite the concomitant increase in transfusions. The lack of a consensus definition of TRALI lead the National Heart, Lung, and Blood Institute to form a working group to delineate TRALI and create a common clinical definition. A Canadian Consensus Conference provided a similar forum and the resulting definitions of TRALI are similar.

The PMN is the effector cell in TRALI; however, neutropenic patients have been reported to develop TRALI, which has been associated with the infusion of vascular endothelial growth factor, a known permeability agent. Because antigen:antibody pairing alone is not sufficient to cause TRALI a two-event model was proposed. The first event is related to the clinical condition of the patient including: recent cardiovascular surgery, active infection, or induction therapy for hematological malignancies, induces pro-inflammatory activation of the pulmonary endothelium resulting in the adherence/pulmonary sequestration of PMNs, which are functionally hyperactive. The second event is the transfusion of donor alloantibodies or biologic response modifiers (BRMs) including bioactive lipids, lysophosphatidylcholines (lyso-PCs) or soluble CD40 ligand (sCD40L) which accumulate during routine storage of cellular blood components and activate these hyperactive, adherent PMNs resulting in endothelial cell (EC) damage, capillary leak and ALI. In addition, platelets appear to be essential for TRALI pathogenesis because in murine models of TRALI, aspirin pre-treatment significantly inhibited anti-body mediated ALI.

Recent investigations have focused on the clinical condition of the patient (first event) at the time of transfusion. A recent study comprised of patients (150) admitted to the intensive care unit for gastrointestinal (GI) bleeding demonstrated that 15% (22) developed TRALI, with fresh frozen plasma being implicated in 86% of the cases. Moreover TRALI incidence in patients with end stage liver disease with GI bleeding was 39% indicating that TRALI may be unrecognised in the critically ill. In addition, patients with recent surgery, especially cardiovascular surgery, patients with hematological malignancies in the induction phase of chemotherapy, and the massively transfused have been shown to be predisposed to developing TRALI. This data indicates that the patient's clinical condition is important for the development of TRALI.

TRALI mitigation efforts, using antibody-negative or male only plasma transfusion practices have significantly decreased both TRALI-related deaths and the total number of TRALI reactions related to the infusion of donor antibodies. However, to date, there are no mitigation efforts for TRALI attributed to the transfusion of packed red blood cells or TRALI induced BRMs, antibody negative TRALI, from stored cellular components.

There are a number of clinical manifestations attributed to the transfusion of stored blood, particularly packed red blood cells (PRBCs) and with the average storage of PRBCs between 17 and 21-days in the USA, a number of large randomised controlled trials have been initiated including the RECESS trial in the US and the ABLE study in Canada and Europe. A two-event in vivo model of TRALI was developed in which rats were pre-treated with lipopolysaccharide (LPS) to mimic active infection followed by transfusion of the plasma from day 1, 28, and 42 PRBCs both pre-storage leucoreduced (LR) or unmodified. The plasma from day 42 Leucocyte –Reduced (LR)-PRBCs, the last day they may be transfused, elicited the most ALI and implicated BRMs, both lipids and sCD40L, as important in the genesis of TRALI. Since current TRALI mitigation is only for products with high plasma volumes, PRBCs are becoming increasingly implicated in TRALI and older stored PRBCs contain large amounts of BRMs which accumulate during their routine storage and are attractive candidates to mediate the second event in the two event pathogenesis. This study also confirmed that antibodies also caused TRALI as the second event in LPS pre-treated animals but not as a single agent.

Transfusion is the most common inciting event to the development of acute respiratory distress syndrome (ARDS). Related studies of ALI/ARDS highlight possible mechanisms important for TRALI pathogenesis. These studies describe the role of lung surfactant proteins interacting with increased levels of cholesterol and other oxidised lipids, e.g. LPC resulting in ALI. Surfactant proteins A and D (SP-A and SP-D, respectively) have been found to mediate the immune functions in lung tissue, with SP-A as an opsonin to induce pro-inflammatory activation of innate immunity mediating lung inflammation. In addition, surfactant proteins B and C (SP-B and SP-C, respectively) decrease the tension across the alveolar surface through their interaction with lipids. A recent study involving the stimulation of genes in cultured human tissue has revealed that the surfactant proteins are synthesized by type II cells of the alveolar epithelium and that under stress or hypoxia the production of these proteins may be decreased.

TRALI is multi-factorial; however, it appears that a two-event pathogenesis is relevant and the final common pathway involves pro-inflammatory activation of the pulmonary endothelium leading to sequestration of PMNs followed by activation and release of the microbicidal arsenal of the PMNs. In short, TRALI appears to be the inappropriate activation of innate immunity which is designed to effectively eradicate infections but can instead induce ALI.

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# Safe Supplies – The Role of Epidemiology in Monitoring Infections

In 1995 a surveillance programme was set up to monitor infections detected through the routine testing of blood donations and among patients receiving transfusions. This programme was jointly funded by the then National Blood Service and the former Public Health Laboratory Service (currently the Health Protection Agency (HPA)). This programme is now managed by the joint NHSBT/HPA Epidemiology Unit and employs a small team of people based at both NHSBT and HPA sites in Colindale, north London.

The original surveillance programme was designed to gather detailed laboratory and clinical information about the infection(s) detected in both blood donors, and blood recipients. The surveillance of both bacterial and viral infections in transfusion recipients forms a major part of SHOT, the UK haemovigilance scheme.

The initial aim of the programme was to contribute to the safe supply of blood by informing donor deferral and testing policies and minimising the risk of transfusion transmitted infections. Since its inception, the programme has continually evolved to accommodate changes in testing practices – such as the introduction of new microbiological tests e.g. hepatitis B nucleic acid testing NAT, and expanded to include other donors – such as surgical bone and deceased tissue donors. The current programme now includes systems for horizon scanning for emerging infections of potential importance to the UK blood services. In addition, the results of microbiological screening of antenatal samples performed by NHSBT have been reported to the programme since 1999, and will end with the NHSBT withdrawal from this service in 2011. During early 2011 NHSBT will introduce routine bacterial screening of platelets and the unit plan to provide monthly surveillance data on contamination rates.

Although NHSBT provides blood for England and North Wales, the unit collects data from all the UK blood services and the Republic of Ireland. The unit relies on data provided by colleagues in the screening and reference laboratories and clinical colleagues throughout the UK.

## *Outputs and Collaborations*

Each year the NHSBT/HPA Epidemiology Unit produces over 100 reports. These are distributed widely to colleagues within the UK and Irish blood transfusion services. Some of these are weekly or monthly summaries of microbiological testing data about donations or antenatal samples and are intended for short-term performance monitoring. Others include more detailed


six-monthly or annual epidemiological data about donors, potential donors or recipients and have a broader use throughout the UK and Irish blood transfusion services, the HPA as well as others with an interest in public health. Most reports are also available to the general public via our webpages: http://www.hpa.org.uk/Topics/InfectiousDiseases/ReferenceLibrary/BIBDReferences/

The unit also responds to ad-hoc requests for data and information and actively participates in research and development activities relating to the epidemiology and surveillance of infections in blood and tissue donors. Members of the unit participate in teaching and presenting to a range of audiences including clinical and scientific staff within haematology and the wider public health workforce. The unit collaborates with other professional bodies and stakeholders involved in blood transfusion and microbiological safety on an ongoing basis. For example, the HTLV National Register is a long-term cohort study of blood donors and other patients with HTLV infection co-ordinated by the unit in collaboration with the blood services, the Health Protection Agency (HPA) and Imperial College London.

## *The HTLV National Register*

The HTLV National Register was set up when NHSBT began testing all blood donations in England and North Wales for HTLV in August 2002 and is ongoing. Little is known about HTLV-associated disease in Europe as this is an infection more associated with individuals living in parts of Africa, S. America and Japan. People are rarely tested for HTLV unless they have symptoms suggestive of HTLV, are relatives of HTLV positive patients, or donate

blood. The introduction of testing provided a unique opportunity to collect information on a group of HTLV infected individuals as they were diagnosed and in collaboration with specialist clinical colleagues follow them up over time. This study hopes to investigate the signs and symptoms of disease over time and gain information on the progression of HTLV in this group of patients, currently the HTLV National Register has over 150 participants.

Further information on the HTLV National Register can be found at: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/BIBD/HTLVNationalRegister/

## *Implications for Policy and Future Service Development*

Epidemiological data about donors and recipients are distributed widely throughout the UK blood services and elsewhere, contributing to policy and service developments within transfusion and transplant practises. The data is also used to formally evaluate transfusion practices; one example is the calculation of residual risk estimates to calculate the risk of HBV, HCV, HIV or HTLV infected donations being released for issue. These rely on surveillance data and are used to determine blood and tissue safety with respect to the likelihood that the current testing methods could miss a potentially infectious donation, which could then be released into the blood and tissue supply. This approach has been developed by the unit to evaluate the benefits of potential new testing techniques (such as nucleic acid tests), new assays (such as for HTLV) and donor deferral policies (such as that relating to men who have sex with men). During 2009 work began with colleagues in the Statistics and Audit department of NHSBT to improve these methods further and explore potential future applications.

The unit also contributes to assessments of potential risks from emerging infections such as the review of donor selection criteria following the spread of West Nile Virus in Italy during 2009.

Data collected from the NHSBT antenatal screening programme have been used to look at immunity to rubella in pregnant women; analyses of this data have implications for policy relating to the vaccination of pregnant women.

The NHSBT/HPA epidemiology unit continue to work with scientific and clinical colleagues to ensure that the data we collect and analyse meets the needs of the UK Blood services and contributes to ensuring a safe supply of blood and tissues.

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# Management of Major Haemorrhage in a Major Trauma Centre

## *Introduction*

Exsanguination is a leading cause of early death following traumatic injury. This accounts for 40% of deaths from trauma and is the most common cause of preventable mortality (Gruen RL *et al* 2006). In the most severely injured patients (injury severity score greater than 25), mortality rates as high as 60-70% have been reported (Spahn DR *et al* 2007). Many of the patients that suffer from uncontrolled haemorrhage do so within the first six hours following injury. This major blood loss is not only a challenge for the trauma surgeon but also to both the haematological and blood transfusion services. In recent years there has been a move towards a more aggressive transfusion strategy with early provision of blood components as part of a goal directed approach to the management of these patients.

## *Definition of Massive Haemorrhage*

Massive transfusion has been arbitrarily defined as the replacement of a patient's blood volume or transfusion of >10 units packed red cell (PRC), over a 24-hour period. Alternative definitions include a 50% blood volume loss within three hours or a rate of loss of 150ml per minute but such criteria may be difficult to apply in the acute clinical setting. It is however imperative to recognise these major blood losses early and implement effective goal directed therapy promptly if one is to prevent shock and its consequences. Early aggressive correction of coagulopathy and optimal resuscitation can help reduce potentially preventable deaths.

The aim of treatment during haemorrhage is the rapid and effective restoration of an adequate blood volume and to maintain blood composition within safe limits. This will allow adequate haemostasis, oxygen carrying capacity, oncotic pressure and blood biochemistry. Massive transfusion itself carries a significant mortality (40%) which increases with the number of units transfused.

## *Acute Traumatic Coagulopathy*

In the most severely injured patients it is well documented that the lethal triad of hypothermia, acidosis and acute traumatic coagulopathy (ATC) are present. Recent work has shown that ATC is present on emergency department arrival in up to 25% of severely injured patients and this is associated with a four-fold increase in mortality. Damage control resuscitation aims to address all components of this triad immediately on admission to the receiving hospital. Both military and civilian studies have suggested improved outcomes with this approach. Damage Control Resuscitation addresses ATC through the empiric and simultaneous replacement of plasma components and packed red blood cells (RBC). There is still controversy over the optimal FFP: RBC ratio with respect to outcomes and haemostatic effects. The optimal ratio of blood components has not yet been identified. Many studies have reported increased survival rates with a 1:1 ratio FFP to RBC. In contrast, other studies have shown that lower plasma doses in a 1:2 or 1:3 ratios have yielded optimal outcomes (Teixeira PGR *et al* 2009). Interim results from a prospective study of trauma patients at our centre requiring > 4 units of RBC suggest that FFP: RBC ratios of >1:1 do not offer any additional advantage over ratios of 1:2-3:4 with the haemostatic benefits of plasma therapy being limited to patients with coagulopathy. Inadequate transfusion is associated with poor outcomes but empirical over-transfusion can result in unnecessary donor exposure with increased rates of sepsis and multi-organ failure.

## *Massive Haemorrhage Policy*

The traditional approach to component therapy in massive transfusion relies on laboratory based coagulation testing but slow turnaround times can lead to inevitable delays. An alternative approach is the empirical use of massive transfusions packs (MTPs) now established as part of the Code Red Massive Haemorrhage Policy at the Royal London Hospital. This is a designated major trauma centre managing >2,000 trauma cases per year with a Helicopter Emergency Medical Service (HEMS).

Audit of our practice in 2007 using MTPs containing four units fresh frozen plasma (FFP), one pool platelets, and two pools cryoprecipitate indicated much over-ordering with excessive wastage. A collaborative revised Code Red Policy agreed between the pre-hospital physicians, trauma surgeons, haematologists and the blood transfusion laboratory was then implemented. This

London's Air Ambulance

aims to allow early identification of patients requiring massive transfusion by early recognition of severe injury and enabling prompt treatment of the emerging coagulopathy to prevent further physiological deterioration. This policy has specific triggering criteria (Figure 1) and facilitates appropriate blood component provision in a timely fashion without undue wastage.

**Figure 1. Code Red Massive Haemorrhage Policy at the Royal London Hospital**

**Management of Massive Haemorrhage and Trauma**
**CODE RED-TRAUMA**

**TRAUMA TEAM LEADER MUST DECLARE CODE RED if:**

- **Systolic BP < 90**
- **Poor response to initial fluid resuscitation**
- **Suspected active haemorrhage**

↓

**Take baseline blood samples prior to transfusion**
Trauma panel including FBC, G&S, clotting screen and fibrinogen
Near patient testing – ABG and FBC

↓

**Immediate Blood Transfusion (red cells)**

- **Use O NEG units in females or O POS units in males**
- **Take emergency blood from RESUS fridge**
- **Immediately inform blood bank resus units are being transfused & request restock. Use direct phone line in resus**
- **Use group specific blood as soon as available**

↓

**ANTICIPATE COAGULOPTHY IN CODE RED PATIENTS**

**Nominated member of team to call blood bank on direct line:**

**State patient's unique identifier and 'CODE RED TRAUMA'**

**Request: ONE CODE RED PACK A**
**(Contains six units Red Cells and four units FFP)**

**Send porter to lab to collect pack immediately**

↓

**If bleeding continues - request ONE CODE RED PACK B**
**(contains: six units Red Cells, four units FFP, one unit; platelets and two pools cryoprecipitate)**

**Continue requesting CODE RED PACK B**
**(one pack at a time) until bleeding stops**

↓

**When bleeding is controlled**

- **REPEAT FBC AND CLOTTING SCREEN**

**Administer further products if**

- **Platelets <80x109/l – 1 dose platelets** (2 doses if plt <30)
- **Fibrinogen <1.0g/l –** 2 pools **cryoprecipitate**
- **APTT/PT ratio >1.5 x normal -** 4 units (~1 litre) **FFP**

**If bleeding persists, contact on call Haematologist to consider rVIIa**

We empirically issue Group O RhD positive RBCs to males to preserve Group O RhD negative units which are used for females and children pending results of blood group testing. The rate of Rh D alloimmunisation may be less common in the context of massive transfusion (Dutton *et al* 2005).

Activation of the Code Red Policy can be pre-hospital i.e. by the HEMS team, within the A&E department and in theatre. If the policy is activated within a pre-hospital setting, blood components can be available upon the helipad within 15 minutes. As soon as the trauma team leader declares Code Red, pack A containing 6 units of RBC and 4 FFP is issued. If bleeding persists a further Pack B is issued containing 6 RBC, 4 FFP, 1 PLT and 2 pools of cryoprecipitate. The trauma team leader would continue to request transfusion packs (Pack B) until the bleeding stops. Parallel to ordering these major haemorrhage packs, blood tests would be ordered periodically. These include FBC, Clotting screen, G&S, Fibrinogen. Near patient testing such as arterial blood gas analysis and FBC are also carried out.

The use of the Code Red policy is continually audited and appropriate changes implemented as necessary following multidisciplinary discussion. The published data from CRASH-2, a randomised control trial examined the effect of tranexamic acid on death, vascular occlusive events and blood transfusion in trauma patients with significant haemorrhage, showed early administration of tranexamic acid reduces the risk of bleeding with no apparent increase in morbidity or mortality *(CRASH-2 trial collaborators 2010)*. As a result, the policy is being amended to include the early administration of tranexamic acid.

We are currently exploring the application of thromboelastometry in guiding component usage in traumatic massive haemorrhage. There is also now much discussion around the role of alternatives to traditional blood components and in particular the use of fibrinogen concentrate for fibrinogen replacement.

In summary, massive haemorrhage contributes significantly to mortality in trauma. An important component in Damage Control Resuscitation is the use of a massive transfusion policy that aids the early identification of patients requiring massive transfusion and enables provision of prompt blood component therapy without excessive wastage.

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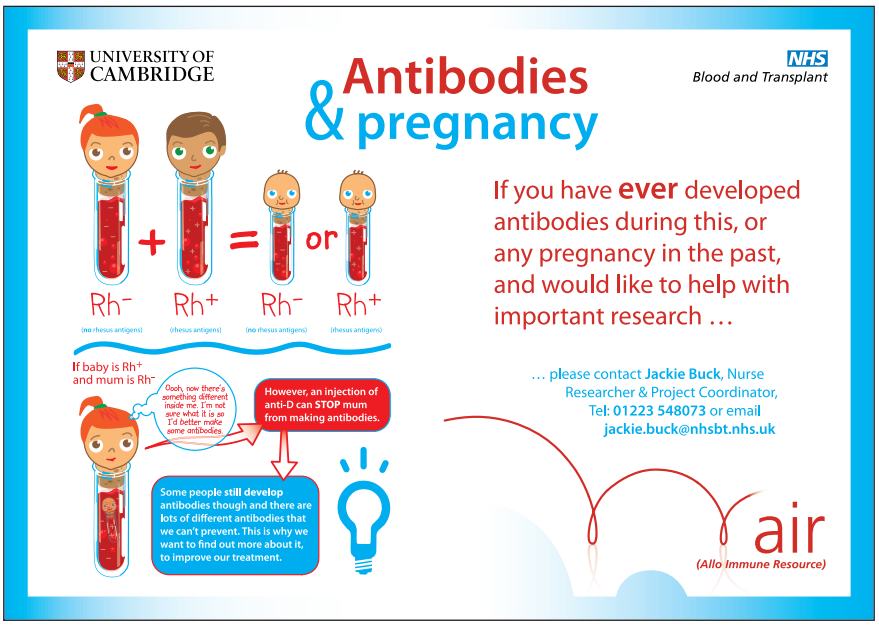
## Understanding Alloimmunisation in Pregnancy: The Air Study




The stakes are high for mothers and babies affected by red cell alloimmunisation in pregnancy. Haemolytic disease of the newborn (HDN) places infants at risk of severe anaemia requiring transfusion but also of rapidly progressive jaundice with the attendant risks of kernicterus and brain damage. For women with significant alloimmunisation during pregnancy, the implications in terms of additional screening, and the risk of fetal loss through hydrops fetalis or as a consequence of invasive therapies are substantial.

Maternal alloimmunisation occurs when a woman's immune system is sensitised to foreign red cell surface antigens, usually during pregnancy with a fetus carrying the sensitising antigen or due to a previous blood transfusion. More than 50 red cell surface antigens can cause HDN but the commonest are in the Rh blood group system. The D antigen is the most immunogenic of the Rh blood group antigens and the system is responsible for most cases of severe HDN. Alloimmunisation against other antigens (including c and Kell) can also cause significant perinatal problems. Sensitisation can occur with even very small episodes of fetomaternal haemorrhage (FMH) at any time during pregnancy but especially in the third trimester and at delivery.

The number of pregnancies affected by HDN varies according to a number of factors. The occurrence of RhD negative individuals is highest in the Caucasian population, with around 16% RhD negative. This means that around 10% of pregnancies in this group are 'incompatible' for RhD. Other ethnic groups have many fewer RhD negative mothers but may have higher proportions susceptible to alloimmunisation due to other red cell antigens. FMH large enough to cause potential alloimmunisation occurs in around 15-50% of pregnancies. Individuals also almost certainly vary in their ability to generate antibodies against alloantigens. Historical data suggests that around 17% of RhD negative women become alloimmunised if they deliver an RhD positive baby, but now that routine prophylaxis is

offered the rate in the UK is thought to have fallen to around 0.35% of susceptible pregnancies. The remaining sensitisation probably occurs in cases where women have not been offered or have declined anti-D but some may still be due to a failure of certain individuals to respond to prophylaxis. There is also a significant burden of alloimmunisation affecting women sensitised against other red cell antigens, for which there is no preventive therapy.

Pregnant women are screened for red cell antibodies when they register for maternity services at 12-16 weeks gestation. Women who have potentially significant antibodies will be recalled for antibody testing and quantification every 2-4 weeks until delivery. In England, NHSBT provides a reference service for identification and quantification of antibodies in these patients. Women who develop significant antibody levels or who demonstrate a rapid rise in antibody levels require specialist clinical assessment including regular middle cerebral artery doppler scanning of the fetus to predict anaemia. Fetuses that are predicted to have anaemia may require fetal blood sampling and intrauterine transfusion (IUT). Serial IUT is often needed in severely affected pregnancies and carries a significant risk of fetal loss. Careful monitoring has led to good perinatal survival and neurological outcomes in the UK (although a number of infants are severely affected or die each year) but the burden of monitoring and invasive therapy is very high in personal terms both for women and for health services.

There is a body of evidence that suggests that the ability to mount an alloimmune response against red cell and platelet antigens is genetically determined. For example, when RhD negative individuals are challenged with large doses of RhD positive blood, around 30% will not generate an anti-D response. This applies as much to pregnancy related alloimmunisation as to that induced by transfusion and transplantation. The idea that there may be 'responder' and 'non-responder' individuals is attractive to investigators because it may allow clinicians to modify treatment according to a more accurate understanding of the risks for any individual. In the case of RhD negative mothers, for instance, if non-responders could be reliably identified then screening and prophylaxis could be simplified. In those alloimmunised for other antibodies, the likelihood of progression to significant HDN could be better predicted. Potential high responders could be closely monitored from early in pregnancy and possibly managed using tailored immunomodulatory techniques rather than high risk procedures such as IUT. Identification of 'high responder' groups could also be helpful to blood banks who might wish to provide closely matched transfusions for those at most risk of alloimmunisation.

The Alloimmune Resource (AIR) has been established by researchers at NHSBT and the University of Cambridge to collect DNA samples and clinical data from individuals with significant alloimmunisation. The first group of patients to be enrolled are women who have developed clinically significant alloantibodies against red cell antigens. We are requesting DNA samples from women who have been referred to NHSBT red cell immunohaematology laboratories for quantification and monitoring of potentially significant antibodies against the Rh blood group antigens and anti-K. In most cases we are able to use the blood sample that has been sent to the laboratory rather than requesting new blood samples. Some women also prefer to provide a saliva sample for DNA purification. Women are contacted by letter and invited to take part, they are provided with information regarding the study and are also able to discuss the study with the study coordinators by telephone. Those women who consent to enter the study are also asked to complete a questionnaire about their medical and obstetric history.

The initial aim of the study is to enrol a cohort of women with clinically significant red cell antibodies whose DNA can be used to identify genetic variations that are associated with a high risk of alloimmunisation. NHSBT and the University of Cambridge have already contributed to numerous genetic studies by establishing (with the help of blood donors) a large, well validated, 'control' population that has been used in many recently reported studies. Our aim is to compare the genomes of our cases with this and other suitable control populations. The study will scan the whole genome and will not specifically focus on individual genes. To complete the first phase of our study we aim to collect samples from 2,500 alloimmunised women. We hope that the work will eventually enable us to identify a number of genes that contribute to the 'high responder' status for alloimmunisation. Knowledge of how each gene contributes to the ability to mount an alloimmune response will have implications not only for pregnant women but also for patients undergoing transfusion and transplantation.

If you, or any pregnant women in your care, would like more information about the AIR study, please contact the study coordinators Nicola Foad nicola.foad@nhsbt.nhs.uk or Jackie Buck jackie.buck@nhsbt.nhs.uk.

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# Coagulation Update: Part 1

The ability of blood to transform itself from a liquid to solid phase is the result of a complex integrated system of procoagulant factors. Rapid and as importantly, localized activity is required to prevent patients from exsanguinating and disseminated thrombosis respectively.

## Initiation of Coagulation

Under resting physiological conditions, the endothelial lining of blood vessels inhibits thrombus formation (Figure 1). Endothelium acts as a physical barrier separating procoagulant factors from reactive subendothelial components and its negative surface charge may also help to repel platelets. Furthermore it possesses anticoagulant properties due to constitutional expression of thrombomodulin and heparan sulphate. Finally it inhibits platelet function by synthesis of prostacyclin and nitric oxide. Coagulation is initiated by a breach in vascular endothelium leading to exposure of tissue factor (TF), a transmembrane glycoprotein. Physiological and pathological mediators including thrombin, tumour necrosis factor and endotoxin may also induce TF expression. TF expression is the pivotal step in transforming the endothelial membrane from an anticoagulant to a procoagulant surface and is facilitated by additional changes including reduced thrombomodulin expression and secretion of plasminogen activator inhibitor (PAI-1).

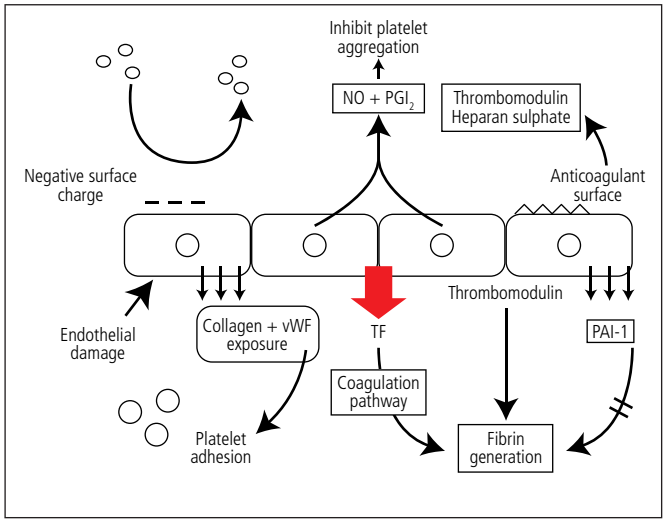


**Figure 1:** *In the resting state (upper surface) the endothelium functions as an effective anticoagulant. Its negative surface charge repels platelets whilst nitric oxide (NO) and prostacyclin (PGI2) inhibit platelet function. Anticoagulant properties are further enhanced by surface expression of thrombomodulin and heparan sulphate. However, after stimulation by cytokines or tissue damage the endothelium rapidly becomes prothrombotic (lower surface). Platelet adhesion is promoted by exposure of subendothelial collagen and von Willebrand factor (VWF). Meanwhile tissue factor (TF) secretion initiates fibrin generation and clot formation whilst fibrinolysis is inhibited by the secretion of plasminogen activator inhibitor (PAI-1). Moreover, anticoagulant properties are modulated by reduced surface thrombomodulin expression.*

Low levels of activated factor VII (FVIIa), a serine protease, are continuously circulating, but when bound to exposed TF the resulting complex is able to activate factors X and FXI leading to generation of thrombin. This is limited to the site of vascular damage by two inhibitors: tissue factor pathway inhibitor (TFPI) and antithrombin. Both regulate TF initiated procoagulant responses. TFPI neutralizes FXa when it is complexed with TF-VIIa. Antithrombin, a serine protease inhibitor, neutralizes the initially formed FXa and thrombin. Consequently coagulation only proceeds if TF is exposed at sufficiently high concentration to overcome inhibition by TFPI and antithrombin. FVIIa thus circulates seeking sites of damage, signalling an alarm by binding to TF. False alarms or excessive responses are prevented by the action of TFPI and antithrombin.

## Platelet Aggregation

Platelets complement and promote the procoagulant pathway and although they circulate in close proximity with the endothelial wall, endothelial adhesion and subsequent platelet aggregation normally only occurs following endothelial damage when not only TF but also subendothelial von Willebrand factor (VWF) and collagen are exposed. Primary platelet adhesion is primarily mediated via the glycoprotein GPIb receptor which binds to VWF. This interaction has a fast association and dissociation rate; thus platelets continue to move constantly in the direction of flow albeit more slowly. During this phase platelet activation occurs and the platelet GpIIb-IIIa receptor undergoes conformational change. The receptor is now able to bind both VWF and fibrinogen resulting in irreversible platelet adhesion and aggregation respectively. The dimeric nature of the fibrinogen molecule allows inter-platelet bridging and growth of the primary platelet clot.

## Platelet Activation

Platelet activation can be induced by a variety of substances but those with greatest physiological relevance include thrombin, collagen, ADP, arachidonic acid and epinephrine. Signal transduction is mediated by G proteins, intracellular cAMP and is calcium dependent.

Platelet activation is accompanied by structural change: the normal smooth biconcave disc shape is lost and platelets become spherical with protruberant pseudopodia promoting interaction between adjacent platelets. Platelet granules centralize secondary to activation of the cytoskeletal contractile apparatus and secretion follows. Release of granule constituents such as serotonin, ADP, VWF and fibrinogen amplifies platelet activation by positive feedback.

In capillaries platelet aggregation together with local vasoconstriction is usually sufficient to achieve and maintain haemostasis. However platelet aggregates are fragile and in larger vessels formation of a fibrin network is needed to generate a firm platelet-fibrin clot. During platelet activation, a reorientation ("flip-flop") of the platelet plasma membrane occurs. Negatively charged anionic phospholipids such as phosphatidlyserine (PS) are exposed on the platelet exterior facilitating coagulation factor binding. Activated cofactor V (FVa) is also expressed. The platelet surface thus provides an efficient catalytic surface for the generation of thrombin at the site of endothelial damage.

## Sustained Procoagulant Response

Coagulation is initiated by activation of trace amounts of thrombin by FXa which is itself activated by TF-VIIa. For effective haemostasis a sustained procoagulant response is needed and is achieved by thrombin activation of factors XI, VIII and V. Although it has been traditional to divide the coagulation system into intrinsic and extrinsic pathways such a division does not occur in vivo because the TF-VIIa complex is a potent activator of factor IX as well as factor X (Figure 2). The initial FXa produced by this mechanism generates sufficient thrombin to induce local platelet aggregation and activation of the critical cofactors V and VIII. However this is insufficient to sustain haemostasis due to rapid Xa dependent inactivation of TF-VIIa by TFPI. Instead marked amplification is achieved by the action of FIXa and FVIIIa. FXIa may be required to produce additional FIXa if insufficient quantities are produced by TF-VIIa or if fibrinolysis is particularly active. The remaining components of the intrinsic system whilst important in vitro do not appear to have an important haemostatic role. The tenase complex (Xa-Va) produced rapidly converts prothrombin to thrombin. Thrombin hydrolyzes the arginine-glycine bonds of fibrinogen to fibrin monomers and activates factor XIII. This stabilizes the fibrin clot through crosslinkage. In addition factor XIIIa may offer further protection from fibrinolysis by linking α2 plasmin inhibitor to fibrin. Thrombin also has a positive feedback role promoting activation of factor XI and cofactors V and VIII thereby ensuring rapid coagulation.

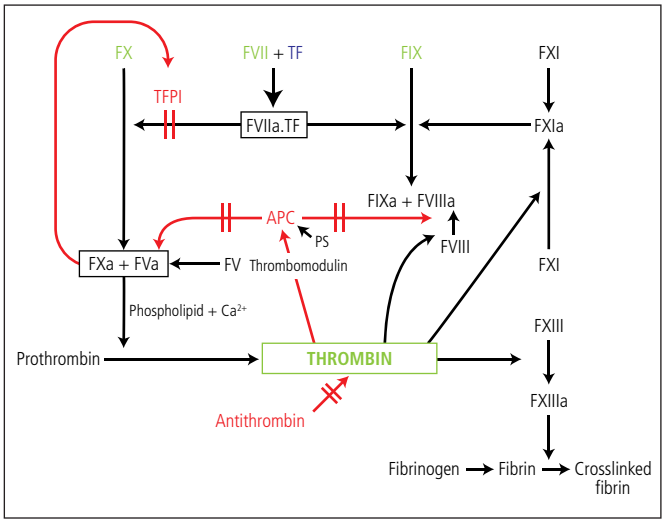


**Figure 2:** *The revised hypothesis of blood coagulation. The vitamin K dependent serine proteases II, VII, IX and X are shown in green with the cofactors tissue factor (TF) and factors V and VIII in green. Tissue factor plays an integral role in the initiation of coagulation through the activation of FVII. Activated factor X (FXa) is generated by the activated factor VIII/tissue factor complex (FVIIa.TF). Due to rapid FXa dependent inactivation of FVIIa.TF by tissue factor pathway inhibitor (TFPI) factors IX and XI are required to generate sufficient tenase complex to ensure thrombin generation. The central role of thrombin is clearly shown. Coagulation is limited by the actions of the anticoagulant system: TFPI, activated protein C (APC) and antithrombin shown in red.*

## Inhibition of Coagulation

The anticoagulant and fibrinolytic pathways prevent excessive procoagulant activity. Antithrombins (serpins) inhibit the serine proteases of the coagulation system whilst the protein C system neutralises activated coagulation cofactors. Antithrombin forms a stable 1: 1 stoichiometric complex with its substrates, predominantly FXa and thrombin. When thrombin binds to surface bound thrombomodulin rather then functioning as a procoagulant it becomes a highly effective anticoagulant. This complex promotes factor C activation by a factor of 20,000. Similarly when cofactor protein S binds to protein C its phospholipid binding potential and hence activity is increased. Activated protein C rapidly degrades Va and VIIIa limiting excessive coagulation

Fibrinolysis is initiated by release of tissue plasminogen activator (tPA) from endothelial cells. TPA converts plasminogen to plasmin, a serine protease. This reaction is promoted when tPA is fibrin bound and is subject to positive feedback: plasmin cleaves tPA into a two chain molecule increasing binding site exposure and promoting complex formation. Plasmin hydrolyses arginine and lysine bonds resulting in proteolysis of fibrinogen, fibrin

and factors V, VIII and XIII. Fibrin and fibrinogen cleavage generates fragments X and Y which inhibit thrombin and fibrin polymerisation respectively. Excessive fibrinolysic activity is itself regulated by inhibition of both tPA and plasmin by PAI-1 and 2-antiplasmin.

Coagulation is thus a tightly regulated homeostatic mechanism ensuring the maintenance of blood flow under physiological conditions but also permitting rapid, localised coagulation in the event of tissue damage. Whilst in vivo the intrinsic and extrinsic pathways are integrated it is still useful to retain this artificial separation for in vitro diagnostic purposes.

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## The Role of the BASK/NHSBT User Group

### *Introduction*

The British Association for Surgery of the Knee (BASK)/NHS Blood and Transplant (NHSBT) User Group was formed in 2002 to promote liaison between the surgeons and the tissue bank at NHSBT with the aim of improving access to, and the quality of, allograft tissue. This is one of a number of user groups set up by NHSBT to provide a forum for professional interaction between the major provider of tissue, NHSBT Tissue Services (NHSBT TS), and the major clinical users of tissue in the UK. The model used for the groups is that used by NHSBT's well established solid organ and ocular Advisory Groups that provide vital links between NHSBT's Organ Donation and Transplantation (ODT) directorate and surgeons and physicians involved in transplantation. The Chair of each user group is a nominee of the appropriate professional association. Group members are clinicians, consultants and other experts from the relevant field, and representatives from NHSBT TS. The groups are managed by NHSBT TS.

### *Aims of the Group*

**The terms of reference for the group are:**

- To collect and report data on the number of soft tissue allograft implantation procedures conducted in the UK and to maintain a database of outcomes.
- To provide a feedback mechanism for clinical outcome data following soft tissue implantation in the UK, allowing comparisons to be made of tissue preserved or decontaminated by different methods.
- To prioritise areas for in vitro and clinical research and development aimed at improving the clinical success of soft tissue allografting in the knee.
- To apply for funding for research and development, where appropriate, and to commission the work when successful.
- To oversee the introduction of new soft tissue allografts, agreeing clinical protocols, establishing user working groups and reporting clinical outcomes to BASK members.
- To make recommendations to NHSBT TS on the range and type of soft tissue allografts to be supplied.
- To monitor and report on novel technologies that might improve the success of soft tissue implantation in the knee, keeping BASK members fully informed.
- To monitor and review the safety of soft tissue allografts in the knee, informing BASK members of the risks involved and recommending risk reduction strategies to NHSBT TS.
- To review the literature in the field, ensuring that BASK members are fully informed of current developments.

As part of it's work, the User Group has initiated a national data collection procedure, which aims to:

- Provide a service evaluation of allografts supplied by NHSBT.
- Gauge the use of allografts in England and Wales.
- Detect early graft failures due to infection or gross mechanical failure.
- Help surgeons review the outcomes of these operations to ensure the grafts that they use are safe and efficacious so patients are given the best possible care and treatment.
- Help surgeons influence the provision of grafts to suit their needs in caring for their patients.

## Data Collection

Five data forms have been developed to examine the outcomes of grafts used in knee surgery:

1 Patient consent

2 Clinical details about the potential recipient of the allograft

3 Pre-operative knee function assessment

4 One year knee function assessment

5 Five year knee function assessment

All NHSBT grafts arrive at the surgical unit with Forms 1, 2 and 3 in the associated packaging. Surgeons introduce the data collection process to the patient and ask the patient to consent to their data being used. This is done via Form 1, which is signed by the patient. Surgeons complete Form 2, a one page document, at the time of the operation. Patients complete Form 3 whilst in hospital for their operation which provides assessments of their pre-operative knee function. Patients are also asked to complete similar assessments one and five years after their operation.

Data Services at ODT are responsible for much of the data entry and validation of data received by NHSBT relating to organ donation and transplantation and has well developed processes in place for requesting follow-up information and chasing outstanding returns. Their expertise in this area is being used to support the BASK/NHSBT User Group in their data collection. All completed forms are returned to Data Services who enter the data into a database, check for outstanding form returns and request missing forms. They also monitor when the one year and five year follow-up from patients is due and send the forms directly to the patients for completion.

## Outcomes to Date

Between September 2008 and August 2010, details of 194 soft tissue allografts supplied by NHSBT were entered onto the database. Clinical and pre-operative assessment details were received for 39% of these grafts. These grafts were used in 69 operations: 10 meniscus, 23 single ligament reconstructions and 36 multi-ligament reconstructions. Follow-up assessments of knee function one year after the operation, due for 29 of the 69 patients, have been received from just eight patients, all of whom reported improvements in their knee function and that there were no infections. Six patients reported that they were satisfied with the outcomes of their operations one year later. Two patients were not satisfied: one because they continued to experience symptoms with their knee; one because their graft snapped in a traumatic injury six months after the operation.

Participation in the data collection is voluntary for both surgeons and patients. It is hoped that as it becomes more established, participation will increase and the majority, if not all, of allograft operation outcomes will be reported.

## Summary

The BASK/NHSBT User Group provides a forum where surgeons can influence the types of tissue allografts that are provided by NHSBT to ensure that they are supplied with the grafts they need to treat their patients. It plays a key part in Clinical Governance, providing surgeons the opportunity to discuss any issues they may have encountered with graft material issued and how they may be resolved. The advice and guidance from the group provides an important contribution towards maintaining standards of allograft tissue supply and transplantation.

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# Complexities and Comparisons: An Update on the Nuffield Council on Bioethics Inquiry on Bodily Donation

The Nuffield Council on Bioethics is approaching the final stages of its inquiry into the donation of human bodily material in medicine and research and will publish its findings in autumn 2011.

The subject-matter of the Council's inquiry – convened in January 2010 and chaired by Professor Dame Marilyn Strathern – is broad and complex. The Council is considering the ethical, social and legal issues raised by the donation of a wide range of bodily material, including whole organs, blood, tissue and gametes, for both medicine and research. It is also looking at volunteering for first-in-human clinical trials – a kind of 'whole body' donation or loan.

This broad approach was adopted in order to allow the Council to examine the complex web of similarities and differences between various types of donation. Distinctions under current UK law include differing degrees of regulatory oversight between, for example, the (living) donation of a kidney, eggs, sperm and blood; and different approaches to the role of payment (permitted only for those participating in first-in-human trials) and to the treatment of expenses and lost earnings (re-funded in full for living organ donors, but capped for egg donors). Other potentially useful points of comparison across the range of material include the invasiveness of the procedure involved and the degree of attendant risks. While the scope of the report may seem dauntingly wide, however, two factors link together all the forms of material being considered by the Council: they all derive from *people*, and they are all being donated with the aim of benefitting *other* people.

One strand of the Council's inquiry is concerned with consideration of why people donate bodily material, and how motivations differ in different circumstances. The question of the role of incentives to encourage donation – whether financial incentives or incentives in kind such as priority for an organ in the future – is increasingly raised in public debate. The Council is considering how far people should be encouraged to donate, and whether some encouragements or incentives might be unethical in themselves, even if they are effective in increasing supply. However, it is also concerned to look beyond the motivations of individual potential donors and consider the role of organisations in soliciting and facilitating donation.

Donation is often presented in terms of a simple relationship from donor to recipient. Such an image is potentially misleading: even where donated material does pass directly from donor to single recipient (as in the case of organ donations), many other 'intermediaries' are crucial to the process. In many other forms of donation (for example tissue donation for treatment or research), the 'supply chain' between the donor and recipient may be long and complicated, extending via a number of intermediaries to many different recipients.

Within this supply chain arise further distinctions between the NHS and the commercial sector, with some donors preferring their material to remain firmly within the NHS. However, the relationships between the NHS and the commercial world are getting ever more complicated, with the NHS relying on medicines produced by the pharmaceutical industry, and the commercial sector relying on bodily material donated within the NHS for its drug development. The interaction and relationships between donors, recipients, commercial operators and the NHS will also be the focus of recommendations from the Council.

The demand for bodily material of various types appears to be ever-increasing. Indeed, there is constant pressure from both healthcare professionals and potential recipients and their families to increase the supply of bodily material to be used for treatment and research. This pressure arises in a climate where the number of people awaiting an organ transplant, and the number of people who die needing a transplant, are well-cited by media and campaigning groups.

In light of these pressures, it may be easy to assume that because there is a demand, supply must rise to meet it, and to sideline consideration of those who donate the material. Central to the Council's concerns, however, is the fact that *people* are the source of bodily material, and for this reason donation could not be, nor should be, value-neutral. The Council is developing an ethical framework which will seek to set out the values to be applied to various instances of donation and volunteering.

To inform the inquiry, a public consultation was held between April and June 2010. It elicited over 170 responses, providing a rich source of opinions, personal experiences, evidence and ideas on bodily donation. A deliberative workshop with 45 recruited members of the public was held to explore the views of people drawn from a cross-section of the UK community. Published academic research and a range of key stakeholders have also been consulted. The Council is consolidating the evidence and opinions it has gathered, and will publish a report with recommendations for policy and practice in autumn 2011.

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# Vigilance and Surveillance of Substances of Human Origin (SOHO V&S) – Developing a Common Approach in the European Union

## *Introduction and Background*

Directive 2004/23/EC, and its associated Commission Directives 2006/17/EC and 2006/86/EC, require EU Member States (MS) to nominate Competent Authorities with responsibilities for the implementation of a series of regulatory activities in the field of human tissues and cells for transplantation and for assisted reproduction. A key function that must be put in place in each MS is a system for vigilance and surveillance (V&S) of these activities, with reporting and investigation of serious adverse events and reactions. Surveys conducted by the Public Health Directorate of the European Commission and presented to the Competent Authorities meetings indicate that many MS are establishing new Competent Authorities and most are developing new systems for V&S in this field. This was confirmed during the EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments) project (Fehily *et al*. 2007, Fehily *et al*. 2008). A review of tissue and cell V&S systems, conducted as part of the EUSTITE project in 2007, indicated that only two MS had well developed systems, namely France and UK; all the others were adapting related vigilance systems or developing new systems and procedures.

Vigilance in this field is complicated by the broad scope of application, the degree of importation from third countries and distribution between EU MS and the mixture of public and private sector service providers.

## *Building on the Work of EUSTITE*

EUSTITE was a three-year EU-funded project that was completed at the end of 2009. The project promoted standardisation of inspection and vigilance across the EU through the development of common inspection guidelines, vigilance tools and training for Competent Authority officials in these activities. The vigilance tools included:

- Criteria for reporting Serious Adverse Events (SAEs)
- A Severity grading system for Serious Adverse Reactions (SARs) with guidance on which level to report
- An Imputability grading system for SARs
- An Impact grading system (risk matrix including wider system implications) for SAEs and SARs.

The tools were tested during a one year pilot study involving 20 MS. Over 300 reactions and events were reported to the pilot and evaluated using the tools. The tools were amended following the pilot and are currently in use in many MS. In its final recommendations, the project identified V&S as a field that needed considerably more work at an EU level. A number of areas were identified and formed the basis of a new project proposal, 'Vigilance and Surveillance of Substances of Human Origin (SOHO V&S)' which was granted EU funding and was launched in March 2010.

## *SOHO V&S Project Objectives*

The project is working to develop a shared view of how serious adverse events and reactions associated with tissue and cell donation or human application are reported, evaluated and investigated. It aims to address harmonisation of terminology and documentation and a consensus on how information should be exchanged between EU Member States, the European Commission and third countries.

## *The Team*

As with the EUSTITE project, SOHO V&S is being co-ordinated by the Italian National Transplant Centre (CNT). It has a Steering Committee and a large number of collaborating partner organisations, including all of the major European professional societies in the field.

## *Steering Committee*

- National Transplant Centre, Italy (Project Coordinator)
- Donor Action Foundation, Belgium
- Irish Medicines Board, Ireland
- National Transplant Organisation, Spain
- Biomedicine Agency, France
- French Agency for the Safety of Health Products, France
- National Centre for Tissue and Cell Banking, Poland
- Human Fertilisation and Embryology Authority, UK
- Human Tissue Authority, UK
- World Health Organisation, Switzerland.

The involvement of the World Health Organisation and many collaborating partners from outside the EU will ensure that the guidance produced in this project reflects international needs and realities, in the context of global movement of human tissues and cells for human application. The Human Tissue Authority in the UK is responsible for dissemination of the project's outputs throughout its duration, including a final conference in the UK in 2012. The Donor Action Foundation acts as internal project evaluator and will maintain contact with two external peer reviewers.

## Vigilance in Assisted Reproduction

Although the EU Directives include gametes and embryos in their scope, it appeared during the EUSTITE vigilance pilot that the directive definitions and the EUSTITE tools were not fully adapted to the field of assisted reproduction and the reporting requirements are interpreted in different ways in MS. The definitions for adverse reactions and events focus on situations that lead, or might lead, to 'the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or prolong, hospitalisation or morbidity'. This does not take into account adverse incidents in the field where the chance of pregnancy is lost due to loss of gametes or embryos. Specificities of assisted reproductive technology, related to the characteristics of the human products involved or to the patients involved (couple), make it necessary to adapt or improve some of the EUSTITE deliverables. A SOHO V&S work-package led by the French Biomedicine Agency is exploring these issues with the active participation of the European Society for Human Reproduction an Embryology, ESHRE. The group is amending the EUSTITE vigilance tools to make them more relevant to the field and developing guidance for EU vigilance in assisted reproduction.

## Illegal and Fraudulent Activity

Up to now, most EU Competent Authorities for tissues and cells have focused their efforts on putting in place systems and procedures to implement the regulatory functions that are required by the tissues and cells Directives, notably inspection, authorisation and vigilance. Many, however, lack experience and training, as well as procedures to follow, for the investigation of cases where illegal or fraudulent activity is suspected. A SOHO V&S work-package led by the French Agency for the Safety of Health Products is gathering information from Member States on cases that have been investigated and concluded, in some cases with enforcement action. The work-package aims to develop guidance, including tools and recommendations, to support all Member States in this particular area of work.


## Notification and Investigation Guidance

The need for common guidelines on the investigation of adverse reactions and events was identified during the EUSTITE project and will be delivered by two work-packages in SOHO V&S. CNT will lead the group developing investigation guidance, using the outputs of a global initiative involving WHO, CNT and this project. The Polish partner is leading a work-package that explores the critical role of hospitals and clinics where tissues and cells are applied to patients; the work-package is developing guidance for ensuring traceability and for detecting, investigating and reporting suspected and confirmed events and reactions at the clinical level.

## Training

In the later stages of this three-year project, the Irish Medicines Board will lead a work-package delivering training, based on the various principles of good practice identified and documented by all of the work-packages. The courses will be delivered following the successful model developed in the EUSTITE project, with a combination of e-learning followed by a residential module.

## Conclusions

An effective vigilance and surveillance system plays a pivotal role in enhancing the safety of tissue and cells for human application. In some cases it facilitates rapid intervention by professionals or regulators to prevent further harm. In general, it ensures the sharing of invaluable information to support improvements in systems and procedures for the benefit of donors and patients. The SOHO V&S project aims to maximise this learning opportunity through international collaboration between regulators and professionals.

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*Further information and updates on the project can be found at http://www.sohovs.org*

*The SOHO V&S project is supported by co-funding from the Department of Health and Consumer Protection of the European Commission. Grant agreement n. 20091110*

## New Developments in Regenerative Medicine

Regenerative Medicine aims to replace a damaged or diseased tissue or organ with a transplant which will become incorporated into the recipient, becomes re-populated with recipient cells and then grows and repairs itself as part of the recipient. By doing so, it raises the possibility that only one transplant will ever be required which is particularly important when transplants are given to children who generally require further operations as their tissue and organs grow.

If a tissue fails or becomes damaged beyond repair, a surgeon has limited options; the damaged tissue can be removed and replaced with another tissue from the same patient (an autograft), it can be replaced with a tissue from a donor (an allograft) or sometimes it can be replaced with a synthetic material. Replacement with an autograft is the "gold standard" but this requires an additional operation to remove the graft with potential donor site morbidity and often it is not possible to obtain enough or any autograft therefore, allografts and synthetic replacements are more commonly used. One problem with allograft tissue is that it contains donor cells, either alive or dead; these can induce an inflammatory response and thereby slow down or prevent full incorporation into the recipient. Regenerative Medicine uses techniques of tissue engineering to remove the donor cells, leaving a decellularised natural tissue scaffold which retains its structural strength and biological properties and due to the nature of the decellularisation procedure, the pores left behind by the removal of the cells are of the correct size and shape for recipient cells to move into.

Regenerative Medicine is a reality. In the past two years, decellularised tissues have been transplanted into patients both with and without the patient's cells being added first. These procedures often have a multi-national team and UK scientists and clinicians are at the forefront.

Human heart valves, decellularised using methods developed by scientists at the University of Leeds and NHS Blood and Transplant Tissue Services, have been implanted into patients in Brazil. Initial studies using 46 patients showed that after a four year follow up the heart valves were functioning normally and without any complications (Thirteen years experience with the Ross Operation, FD da Costa *et al*, J. *Heart Valve Disease;* 18:84-94, 2009). During the follow up a biopsy showed that although the transplanted tissue had been decellularised it had become colonised and re-populated by recipient cells. The study has been extended to include at least 150 patients, including children and more complicated operations, with similar success.

UK scientists have also been involved in two recent transplants of trachea (windpipe) where the patients' own stem cells were added first but in different ways. In November 2008, a team of clinicians in Spain reported transplanting a trachea, obtained from a deceased donor and decellularised, into a 30 year-old female in June 2008. Before transplant, the trachea was transported to Bristol where Professor Anthony Hollander incubated it in a bioreactor in the presence of the patient's own cells – epithelial cells to line the trachea and cartilage cells to grow into the trachea. Cleverly, the two cell types were added at the same time, in a bioreactor designed to keep epithelial cells on the inside and cartilage cells on the outside. (Clinical transplantation of a tissue-engineered airway. P. Macchiarini *et al*, *The Lancet;* **372**: 2023-2030, 2008). The decellularisation process took three months but in 2010, the team have reported reducing the processing time to three weeks.

One of the UK surgeons involved in the Spanish transplant, Professor Martin Birchall performed a tissue engineered tracheal transplant in Great Ormond Street Hospital in March 2010. In this case the patient was a 10-year old boy suffering from Long Segment Congenital Tracheal Stenosis; the length of trachea was the largest ever transplanted and stem cells were added to the tissue just four hours prior to the transplant. The stem cells were obtained from the boy's bone marrow with the aim that they would lodge in the trachea and form the appropriate cells in the body. As well as reducing time, the more recent technique has also significantly reduced costs of the procedure.

What is the future for Regenerative Medicine? There are currently 1,000 commercial companies and hospitals worldwide which use tissue engineering techniques to develop cell and tissue based products to treat cancer, heart disease, diabetes, neurologic disorders and movement disorders. Transplantation of whole organs and tissues have proved successful and work is being performed on decellularising the range of tissue suitable for transplant. Further work is now beginning to look at ways of inducing repair without the need for transplant by injecting stem cells or cells already differentiated into appropriate tissue types to the site of repair. The cells can be injected directly but to reduce the possibility of cells being washed away from the repair site, they can be injected inside gels (hydrogels) which may also contain bioactive factors to stimulate new tissue formation at the damaged site.

Regenerative medicine opens up the possibility of replacing almost every damaged or worn out tissue with a new tissue capable of becoming part of the patient and returning normal functionality. Whether these new tissues allow a longer active life, remains to be determined.

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## Obituary: Dr Bernard Loty (1953 – 2010)

Bernard Loty was born on January 14, 1953 in Paris. He completed his studies at the Faculty of Medicine Xavier Bichat in 1985 and chose to move to orthopaedic surgery. Appointed Head of the University Clinic in Cochin, Port Royal, his interest in practical applications in the biomedical field lead him to a Master of Biological and Medical Engineering in 1988.

He worked as an orthopaedic surgeon in the service of Professor Postel, then Pr Tomeno at the Cochin Hospital, until 1994. Early on, he showed his interest in the storage of bone and was among the founders in 1988 of the Association for the Study of Transplants and Substitutes in Orthopaedic Tissues (Gesto), that he chaired from 1990 to 1995. Until 1995 he managed the first bone bank created by the "Assistance Public", at Cochin *(Text Extracted from the ABM website).*

In 1999, he joined the French establishment of transplants and provided new impetus to this institution in its role in the development of "services for regulatory support" (hospital coordination) in the area of procurement and transplantation of organs, amongst others.

I knew Dr Loty while I was working at the French Health Products and Safety Agency (AFSSAPS). I was responsible for the inspection unit in charge of the inspection of tissue and cell banks and he was working at the "Etablissement Français des Greffes" which in 2005 became the Agence de la Biomédecine.

I had many meetings with Dr Loty in the framework of the authorisation of tissue and cell banks in France. The missions entrusted to Etablissement Français des Greffes included promotion of organ donation, the rules relating to the distribution of organs, tissues and cells, management of

the register of non-objection to donation, support to health care facilities performing procurement and transplant of organs and tissues.

At that time we had different roles with Bernard Loty supporting the tissue establishments in achieving authorisation and further development of their activities, whilst my tasks were to control compliance by tissue establishments with existing national regulations. We often had diverging views on technical and regulatory points of interpretation and application, but this only increased the respect and friendship I had for him.

Dr Loty always took things to heart to defend the dossiers for which he was responsible at both national and international levels. He was a principal architect of the French Good Tissues and Cells Practices published in 1998 and more recently the Tissues and Cells Directive (2004/23/EC).

He represented France in many institutional working groups of the European Commission and Council of Europe, where he became Chair of the Working Group on Organ Transplantation from 2005 to 2009.

His temperament was well known and accepted by professionals with whom he worked. That personality (always flooded with a huge sense of humour) was also his strength when needed to support and defend difficult and important dossiers in the field of transplantation. We cannot count the number of professionals to whom he provided advice, opinions and support, especially the tissue and cell banks which he accompanied in the long process towards authorisation of their activities and to help them face AFSSAPS or the Ministry of Health.

Sometimes, when I returned back from a difficult inspection which was likely to result in a probable penalty such as a warning letter, order letter or suspension of a tissue or cell banks, he always called me on my mobile phone (after the inspectees had complained about me to him). He would give me a forceful sermon and try to change the AFSSAPS verdict, through me, regarding the final decision for the tissue establishment.

In this case, the story ended with a meeting between the directors of the Etablissement Français des Greffes and AFSSAPS. During these meetings everyone gave their point of view with the sole intention of finding the best solution without penalising patients awaiting transplantation.

I have very often used his knowledge and experience when I faced difficult situations and this was always freely available. The charms of his personality were his strong temperament, his untiring generosity and also his courage and the firmness of his convictions. I always admired this temperament which helped me to advance in my professional life.

He rarely spoke of his illness as he fought for the interests of patients waiting for transplants. He continued his work for the Biomedicine Agency with the same energy he had always shown until his last moments in June 2010.

Bernard Loty remains one of the leading figures in the organisation of transplantation in France.

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## Adventures in Academia – A Teaching Qualification Experience

### *Introduction*

There is increased pressure from health-based regulatory authorities such as the National Patient Safety Agency and professional organisations to promote formal teaching and competency assessment.

As a doctor I was mindful of my responsibilities, aware of the (modern version of) the Hippocratic Oath which states 'I will… gladly share such knowledge as is mine with those who are to follow'.

A variety of teaching qualifications are available such as a Masters degree, City and Guilds 730 or an A1 Award NVQ. These may or may not be appropriate for each individual, especially when cost and time factors are considered.

Whilst I was a source of reference, expertise and support I did not, however, possess much insight into the theory and practice of teaching and learning. By chance, whilst browsing the University of Exeter website for my other day job with the medical school I discovered details of a short course which offered a useful qualification as Associate of the Higher Education Academy (AHEA). The added attraction was that it was free of charge!

### *Background*

The Higher Education Academy (HEA) is recognised by and works with many Universities and Colleges in the UK to develop and promote evidence-based practice for teaching and learning.

My local University, the University of Exeter, offers the

AHEA as part of their Learning and Teaching in Higher Education (LTHE) programme. This is aimed mainly at Postgraduates, but participation from those outside academia is strongly encouraged.

There are two stages:

– Stage 1 (Introduction – basic principles) one day, certificated
– Stage 2 (In depth learning) – 6x2hr sessions, certificated

There is then the option of assignment writing (5,000 words), based on reflection of the teaching and assessment role, together with evidence of peer observed teaching. The timescale for completion is six months. Only when the assignment is passed can the AHEA be awarded, although it is possible to attend just Stage 1 and/or Stage 2.

There were various logistical processes to be addressed.

My first task was to approach my manager for approval. I had to consider time away from my hospital work not only for the course (1100-1300) but also for travel time (3/4 hour each way). Continued professional development is very much encouraged in our Trust, with the added bonus that blood safety and conservation is recognised and respected. I was lucky that the course day was a Wednesday, my protected 'Transfusion Day'; although I was informed by my manager that it would not have been a problem if this had been scheduled for another day. My application was therefore swiftly and positively finalised.

I was offered study leave for the course, but in fact used this only for the assignment writing, preferring to catch up on the time missed for Stages 1 and 2 during other times in my working day. There was about an hour's study time each week which I did either in the evening or at weekends.

Application for the course was online, via the University of Exeter website, and very straightforward.

I was not accepted at the first application because the course was over-subscribed, but managed to gain a place six months later.

The course was well-organised, varied, interesting and relevant. I enjoyed learning in a peaceful area outside my comfort zone.

It made me think about how I approached my teaching and assessment.

I was the only 'non-academic', and a medic, as the other participants were Postgraduates eager to learn about useful teaching principles and gain a qualification in the process. I was nevertheless welcomed and became known (I think affectionately!) as the 'loose cannon'. This was perhaps because I came from the NHS, I offered a different and sometimes a more practical outlook and I was not afraid to challenge.

I learned a lot about the theory of teaching and assessment – how important it was to consider your target audience, their learning needs and competencies and their often varied environment. Different types of learning were taught and discussed; traditional face-to-face lecture style, practical workshops, e-learning, electronic interactive anonymised audience participation to name a few examples of blended learning.

There was a whole new terminology to learn, but this was patiently and repeatedly described.

I learned about tailoring my teaching to the assessment outcome (constructive alignment) which I used to good effect for writing my Trust e-learning module for Transfusion.

All this was good, so what was bad?

The worst part was trying to get away from work in time for the course! There was also the problem of catch up, so a few late evenings ensued. As someone who was used to critiquing scientific papers, I found some of the evidence confusing and lacking in depth, although I acknowledge that I was very much on a learning curve during this process.

Stage 1 was good preparation for Stage 2 which in turn provided the setting for assignment writing.

The LTHE tutors provided excellent support, verbally and also via the website blog, to which we classmates could contribute.

Many of us proceeded to the assignment writing; as before there was tutorial support provided together with good examples of others' past (and passed!) work on the website. We were assigned a Tutor according to our background – arts, law, science, engineering and the NHS.

I was informed by email six weeks later that I had been successful. My assignment was returned to me accompanied by constructive comments from my tutor and also the Head of Department. A month later I was sent my certificate directly from the HEA, with an invitation to keep in touch with them and help facilitate closer links with colleagues who share commitment to teaching and learning – hence this article.

## *Conclusion*

Professional recognition is a useful adjunct to your continued professional development portfolio and is a valuable portable asset.

The AHEA qualification is recognised across the higher education sector as evidence of expertise and

commitment to enhancing student learning.

Many institutions link recognised status to internal recognition, reward and promotion processes.

Was it worth it? – Yes, for all the reasons as described above. In addition the course is relatively short compared with other qualification seeking procedures.

Would I recommend to others? – Yes I would.

Look for similar adventures at a College or University near you!

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**References**

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"The Hippocratic Oath: Modern Version". Doctors' Diaries. WGBH Educational Foundation. http://www.pbs.org/wgbh/nova/doctors/oath_modern.html

Higher Education Academy http://www.heacademy.ac.uk/

## Famous Lives in Blood Transfusion – Rob Race and Ruth Sanger

Robert Russell Race started his career in blood grouping in 1937 when he answered an advert in the BMJ saying, "Assistant serologist wanted, must be medically qualified" and subsequently joined a small research unit at the Galton Laboratory, University College London, led by the geneticist and biomathematician R A Fisher. The unit moved to Cambridge at the outbreak of war and it was there that Race and Fisher worked out the basis of the Rh blood group system and established the CDE terminology, with much of the analysis of their serological data taking place in a Cambridge pub called the Bun Shop. Race and Fisher proposed that the Rh blood groups were governed by three closely-linked genes, a theory vehemently and bitterly attacked by Wiener in New York, who believed that there was only one Rh gene. Although half a century later molecular genetics revealed that only two genes are involved, Race and Fisher's synthesis was correct according to the concept of a gene at that time. In 1958 Race and Sanger wrote, "The existence of three sites where Mendelian substitution can go on seems to us unassailable, and to argue whether the three sites are to be placed within or without the boundary of one gene appears particularly unprofitable at the present time when no one seems to know what the boundaries of a gene are".

In 1946 the Medical Research Council established the Blood Group Research Unit at the Lister Institute in Chelsea, London with Race as director. The same year Ruth Sanger, who was working at the Red Cross Blood Transfusion Service in Sydney, travelled to London from her homeland Australia to gain experience in blood group serology at Race's Blood Group Unit. After completing a PhD and a brief return to Sydney, Ruth came back to the Blood Group Unit in 1950, the same year as publication of the first edition of Race and Sanger's *Blood Groups in Man*. Rob Race and Ruth Sanger were married in 1956. When Race retired in 1973, Ruth Sanger took over as director of the Blood Group Unit, which then moved

from the Lister Institute in Chelsea Bridge Road to Wolfson House, an annex of University College London. This was also a move away from the Rising Sun public house, where Ruth and Rob shared many working lunch hours with the numerous visitors who passed through the lab. Rob Race was elected a fellow of the Royal Society in 1952 and Ruth Sanger was elected in 1972.

Between 1950 and 1975 Race and Sanger published six editions of *Blood Groups in Man*, the blood groupers' bible. During that period this was the only textbook any blood group serologist required. It was also used extensively by human geneticists as during this period red cell surface antigens occupied a key position in the study of human genetics. In the preface to the sixth edition Race and Sanger wrote, 'Here is the last edition of this book: the subject has grown to need more than our two pencils'. The field was moving into the biochemical era. They felt that their understanding of biochemistry was limited and they would not write about anything they did not fully comprehend. *Blood Groups in Man* was full of information, academic insight, and, in places, characteristic wit, such as the reasons given for a lack of suitable anti-H reagents: "Humans with good anti-H in their serum were too rare, eels too difficult to handle and *Lotus tetragonolobus* too awkward to pronounce". The book also contained items of unexpected biological information, such as in the section on skin grafts between chimeric twins. "The nine-banded armadillo is apparently born regularly in sets of monozygotic quadruplets. It was doubly surprising to learn that skin grafts are not accepted between a set of quadruplets: the first surprise was to read that armadillos have skin."

Race and Sanger's contribution to blood group research over 46 years was vast. During those years they were involved in the discovery or expansion of 17 of the human blood group systems. Their research extended into many applications of blood groups to problems of human genetics. These included mapping the genome, such as estimating the distance between the genes for Lutheran and ABH secretion, the first recognised human autosomal linkage. Following the discovery, at the Blood Group Unit, that $Xg^a$ was an X-linked blood group, their work made a substantial contribution to the mapping of the X chromosome and to the understanding of sex chromosome aneuploidy, maleness in the absence of a Y chromosome, and X chromosome inactivation. The contribution of cell surface markers provided a foundation to the molecular approach to human gene mapping that has led to the sequencing of the human genome.

Despite their eminence, Rob and Ruth were very friendly and warm people. Rob Race was a quiet and thoughtful man, whereas Ruth Sanger was much more outgoing. Visitors from all over the world who had an interest in blood groups or human genetics were always made welcome at the Blood Group Unit.

Race and Sanger, together with the other pioneers of blood group serology – Landsteiner, Levine, Wiener, Marsh, Issitt, and Tippett to name just a few – certainly played a vital role in making blood transfusion safe. Most of their work was based on interpreting patterns of serological reactions, but the information they obtained has been the bedrock of subsequent research into the red blood cell and into the pathology resulting from malfunction or parasitic invasion of those cells.

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# Next Edition

**Issue 34 will feature articles on:**

- Safe and Dignified: The Donation Chair
- SHOT Reporting and the Role of the Incidents Specialists
- NHSBT Tissue Retrieval Team Training Review 2009 Onwards
- Pioneers in Stem Cell Transplantation – E Donnall Thomas

If you would like to comment on any of the articles in this edition of ***Blood and Transplant Matters*** please email the Editor: derwood.pamphilon@nhsbt.nhs.uk

## CPD Questions

### Understanding Alloimmunisation in Pregnancy: The Air Study

**1. Haemolytic Disease of the Newborn (HDN) can be caused by:**

a) Only by the D antigen.

b) By about 10 red cell surface antigens.

c) By about 30 red cell surface antigens.

d) More than 50 red cell surface antigens.

**2. In the UK, since routine anti-D prophylaxis is offered. The rate of RhD negative women becoming alloimmunised with anti-D is:**

a) 0.35%.

b) 0.5%.

c) 2%.

d) 17%.

**3. The initial aim of the AIR study is to identify genetic variations that are associated with:**

a) A poor alloimmune response against red cell antigen.

b) A high risk of alloimmunisation.

c) A poor response to anti-D prophylaxis.

d) HDN due to non-Rh or K antigens.

### A Cell Salvage Update

**4. The Latham Bowl was introduced to separate plasma from red cells during the:**

a) Korean War.

b) Indonesian War.

c) Vietnam War.

d) Algerian War

**5. Intra Operative Cell Salvage (ICS)**

a) About 70% of Aneurysms are suitable for endovascular repair and do not require ICS.

b) Cannot be used in Urological Malignancy.

c) Cannot be used in obstetrics due to amniotic fluid embolism.

d) Is very rarely used in aortic arch reconstruction.

### Bacterial Screening of Platelets

**6. Use of diversion pouches and improved arm cleansing has reduced contamination from donor skin by at least:**

a) 20%.

b) 40%.

c) 60%.

d) 80%.

**7. Bacterial Contamination of Platelet components have resulted in:**

a) 4.

b) 6.

c) 8.

d) 2.

..... fatal incidents since 1996.

### Transfusion Related Acute Lung Injury (TRALI)

**8. Was first coined by investigators in:**

a) 1975.

b) 1985.

c) 2000.

d) 2006.

**9. TRALI**

a) Red cell concentrate implicated in most cases.

b) Related deaths have not decreased despite the use of male only plasma.

c) Is unrelated to the patient's clinical condition.

d) Has been vastly under reported.

### Safe Supplies – The Role of Epidemiology in Monitoring Infections

**10. A surveillance programme to monitor infection detected through routine testing of blood donation was set up in:**

a) 1980.

b) 1985.

c) 1990.

d) 1995.

**11. The unit collects data from:**

a) UK Blood Services and Republic of Ireland.

b) UK Blood Services only.

c) England and Wales only

d) NHSBT only.

**12. The HTLV National Register was set up:**

a) In July 2002.

b) In September 2002.

c) When NHSBT began testing donations for HTLV.

d) In August 2003.

### Management of Major Haemorrhage in a Major Trauma Centre

**13. Exsanguination accounts for:**

a) 10%.

b) 20%.

c) 30%.

d) 40%.

..... of deaths from trauma.

**14. Hypothermia, Acidosis and Acute Traumatic Coagulopathy are present in up to:**

a) 25%.

b) 15%.

c) 10%.

d) 5%.

..... of severely injured patients.

**15. Audit of massive transfusion packs showed:**

a) Under-ordering of products.

b) Excessive wastage of products.

c) Appropriate use of products.

d) Justified continued use.

# Diary Dates

## 2011

**9-11 May 2011**

**Blood and Marrow Transplantation (ESH-EBMT Training Course)**

Location: La Baule, France
(80km from Nantes on the Atlantic Coast).
Details: For more information contact:
http://www.esh.org

**11 May 2011**

**Special Interest Group for Transfusion Microbiology**

Location: NIBSC, South Mimms, Herts.
Details: The Special Interest Group for Transfusion Microbiology will hold a meeting at NIBSC, South Mimms, Herts on Wednesday 11 May 2011 from 10.30am – 4pm. Further details on how to find NIBSC are on http://www.nibsc.ac.uk.
For further information visit:
http://www.bbts.org.uk

**12 May 2011**

**BBTS Apheresis and Blood Collection SIG Meeting 2011**

Location: Austin Court, Birmingham.
Details: A day of topical interest and discussion to inform and enliven. Aimed at all those with an interest in Donor Recruitment/Retention, Donor Care, Blood Collection and Donor Apheresis, from any discipline.
DONOR:

- Post donation information and its impact
- Impact of donation related adverse events and re-attendance
- Donor Vigilance – What does it mean?
- Donor expectations – Do we meet them?
- Medico-legal aspects and blood donation – are there any?
- Rare blood donors. Current practice and future developments.
- Old favourites! Iron status and donors; anything new?

DONATION:

- Extended life of platelet units – What is the verdict?
- Viral markers, Malaria screen and its confirmatory tests – an update.

GENERAL:

- Panel Discussion – difficult grey areas and causes.

For more information visit: http://www.bbts.org.uk

**18-21 May 2011**

**11th International Symposium on Myelodysplastic Syndromes (MDS 2011)**

Location: Edinburgh.
Details: You can view the programme and register online: http://www2.kenes.com/mds
The MDS represents an important meeting point for haematologists and MDS experts from all over the world to promote the ongoing exchange of information relating to MDS and is established as the leading forum for the exchange of knowledge in this field.
MDS 2011 will feature a rich scientific program, focusing on such topics as immunopathogenesis, molecular pathogenesis, molecular mechanisms and drug targets, new therapies and transplantation.

**18-21 May 2011**

**17th Annual Meeting**

**International Society for Cellular Therapy**

ISCT

Location: De Doelen Congress Centre, Rotterdam, The Netherlands.
Details: The 17th Annual ISCT meeting will provide educational opportunities for all disciplines within the field of cell therapy. The program includes six plenary sessions on the following topics:

- Mesenchymal Stem Cells
- Cancer Stem Cells
- Embryonic to Adult Stem Cells
- Regenerative Medicine and Tissue Engineering
- Cardiovascular Cell Therapy
- T Cell Immunotherapy.

The program also includes several scientific technical sessions and workshops, as well as two educational tracks: The Strategies for Commercialization Track and The Technical Applications Track.
For more information visit:
http://www.celltherapysociety.org/index.php

**23 May 2011**

**Introduction to Tissue Banking Foundation Course**

**Location:** University Hospitals of Leicester NHS Trust.

**Details:** As part of their ASM, the British Association for Tissue Banking (BATB) is running a course entitled an Introduction to Tissue Banking. This course is a pre-cursor to the Specialist Certificate in Cell and Tissue Transplantation Science but would also be of interest to those already studying for the Specialist Certificate. It is a one-day course, taking place at University Hospitals of Leicester NHS Trust on 23 May 2011. The day is priced at £100.

For more information visit: **http://www.batb.org.uk.**

**24 May 2011**

**BBTS Hospital Transfusion SIG (Special Interest Group)**

**Location:** Austin Court, Birmingham.

**Objectives:** A multi-disciplinary meeting designed to discuss the clinical and laboratory aspects of providing safe and effective transfusion support. The morning sessions will focus on transfusion avoidance strategies and inappropriate use of blood components. The afternoon sessions will explore the challenges of ensuring adequate transfusion to those who require it.

**Aimed at:**

- All medical, nursing and scientific staff who have an interest in blood transfusion and the safe and appropriate use of blood.
- Clinicians and trainees who prescribe blood components in medicine, surgery, obstetrics, and intensive care.
- Biomedical Scientists and trainees working in hospital transfusion departments.
- Clinical Nurse Specialists in transfusion and pre-operative assessment.

For more information visit:
**http://www.eventsforce.net/hot11**

**24-25 May 2011**

**Surveillance and Screening of Blood Borne Pathogens**

**Location:** Radisson Blu Royal Hotel, Dublin, Ireland.

**Details:** IPFA/PEI 18th Workshop on:

- "Surveillance and Screening of Blood Borne Pathogens" in collaboration with the Irish Blood Transfusion Service
- IPFA is the international association representing not-for-profit organisations, responsible for the provision of safe and high quality medicinal products derived from plasma.
- PEI is the German Federal Institute for Sera and Vaccines, that conducts extensive scientific research, and has regulatory responsibility for the quality, safety and efficacy of drugs and blood products.

Further information can be found in the Events Section of the website: **http://www.ipfa.nl.**

**9-10 June 2011**

**SCOTBLOOD 2011**

**Location:** University of Stirling, Scotland.

**Details:** The Scotblood Conference will be held at the University of Stirling on Thursday 9 June – Friday 10 June. Further information and registration can be found at **http://www.scotblood.co.uk/snbts-annual-conference-2011** as well as details of how to submit poster abstracts.

Full details of costs for registration and accommodation can be found on the registration site, as well as contact details for any further information. Alternatively, email: **NSS.scotbloodconference@nhs.net**

**13-14 June 2011**

**Stem Cells and Cardiovascular Disease – from Promise to Reality**

**Location:** Manchester.

**Topics:**

- Stem cells: current knowledge and future hopes.
- From cell physiology to reparative medicine.
- Atherosclerosis: a disease of failed repair?
- Reparative and regenerative medicine: finding a consensus for 21st-century healthcare?

For more information please contact Enquiries on **yvonne.alexander@manchester.ac.uk**

**18-22 June 2011**

**XX1st Regional Congress of the ISBT, Europe**

**Location:** Lisbon, Portugal.

**Website:** http://www.isbtweb.org

**24 June 2011**

**National Transfusion Practitioners Educational Meeting**

**Location:** Holiday Inn, Filton, Bristol.

**Target audience:**

Transfusion practitioners from all backgrounds and of all experience levels. Including Associate Transfusion Practitioners UK wide.

**Aims of the meeting**:

To offer specific TP education to include discussion around the future roles of TPs and to offer networking and support opportunities.

If you would like to register your interest and/or obtain further details regarding this meeting please e-mail Catherine Riley at **events@bbts.org.uk**

**4-7 July 2011**

**Techniques and Applications of Molecular Biology: A Course for Medical Practitioners**

**Location:** Warwick

Warwick University Short Course.

Optional accreditation leads to a masters level Postgraduate Award.

**Details:**

Dr Charlotte Moonan, School of Life Sciences, University of Warwick, Coventry, CV4 7AL

Tel no: 024 7652 3540

Email: **Charlotte.Moonan@warwick.ac.uk**

**Website:**

**http://www.warwick.ac.uk/go/lifescienceshortcourses**

**6 July 2011**

**SHOT Annual Symposium 2011**

**Location:** The Royal Society of Medicine, 1 Wimpole Street, London.

Please contact the SHOT Office for more information.

Email: **shot@nhsbt.nhs.uk** Tel no:0161 423 4208.

**7-10 September 2011**

**BBTS Annual Conference Glasgow 2011**

**Location:** SECC, Glasgow, Scotland.

**Details:** The BBTS Annual Conference is aimed at anyone with a professional interest in the practice of blood transfusion and related medical therapies, from donor recruitment to the clinical and scientific care of recipients.

Anaesthetists and Intensivists – the special focus on clinical transfusion trials and practice will, we hope, be of particular interest to you.

Highlights of the 2011 Annual Conference will include:

- XMRV: the inside story.
- Results from the Focus trial on transfusion thresholds after hip fracture surgery.
- The CRASH2 trial with new information on tranexamic acid and obstetric haemorrhage.
- Updates from the Canadian TRIPICU (paediatric transfusion) trial and the ABLE trial on age of blood.

In addition we have top speakers on platelet transfusion, carbohydrate red cell antigens and the very latest on fetal D typing, and a new session for this year will focus on clinical transfusion case studies.

**Special Interest Group (SIG) sessions**

These will feature for a full day on Wednesday 7th and a half day on Saturday 10th.

There will also be the regular favourites such as award lectures, serological case studies, a nursing/transfusion practitioner symposium, oral presentations of submitted works, further education sessions, and the chance to network with colleagues from across the country.

**Website: http://www.eventsforce.net/asm11**

**8-11 September 2011**

**2011 International Congress on Controversies in Stem Cell Transplantation and Cellular Therapies (COSTEM)**

**Location:** Berlin, Germany.

**Details:** The International COSTEM Congress will function as an exclusive forum for international experts to share and compare experiences, in order to outline the right treatment for patients. This innovative Congress is unique in its explicit focus on resolving controversies in the best clinical care of patients. Academically, the Congress will raise the most dynamic and controversial topics facing clinicians in the field in an exciting and engaging debate forum. The Congress will promote excellence by seeking to shed light on ongoing and challenging debates and to bridge gaps between the expansion of information and its consolidation in clinical practice.

**Website: http://www.comtecmed.com/costem/2011**

**19-21 September 2011**

**Haematology in Obstetrics**

**Location:** Leicester Royal Infirmary, UK.

For more information visit:

**http://www.b-s-h.org.uk**

**22-25 September 2011**
**Chromic Myeloid Leukaemia – Biological Basis of Therapy (ESH-ICMLF International Conference)**
Location: Estoril, Portugal.
For more information contact: http://www.esh.org

**23-24 September 2011**
**ASH State-of-the-Art Symposium (SAS)**
Location: Palmer House Hilton, Chicago, USA.
Details: This annual, clinically focused CME activity is designed to offer the same high quality educational content for which the ASH annual meeting is known.
Website:
http://www.hematology.org/Meetings/State-of-the-Art-Symposium

**14-16 October 2011**
**Acute Myeloid Leukaemia – 'Molecular' (ESH-EHA Scientific Workshop)**
Location: Mandelieu, France.
For more information contact: http://www.esh.org

**22-25 October 2011**
**AABB Annual Meeting and CTTXPO 2011**
Location: San Diego, California, USA.
Details: Learn the latest in blood banking, transfusion medicine and cellular and related biological therapies.
For more information contact:
http://www.aabb.org/events

**7-10 November 2011**
**Thrombosis and Hemostasis (ESH-ISTH Advanced Course)**
Location: Cascais, Portugal.
For more information contact: http://www.esh.org

**17 November 2011**
**NEQAS (UK) BTLP and BBTS Blood Technology Joint Meeting**
Location: Birmingham Motorcycle Museum.
Details: Registration opens June 2011.
For more information visit: http://www.bbts.org

**20-23 November 2011**
**XXIInd Regional Congress of the ISBT, Asia**
Location: Taipei, Taiwan.
For more information contact:
http://www.isbt.web.org

**10-13 December 2011**
**ASH Annual Meeting and Exposition**
Location: San Diego, CA, USA
Website:
http://www.hematology.org/Meetings/Annual-Meeting

## Notes

Blood and Transplant Matters is prepared
and issued by NHS Blood and Transplant,
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