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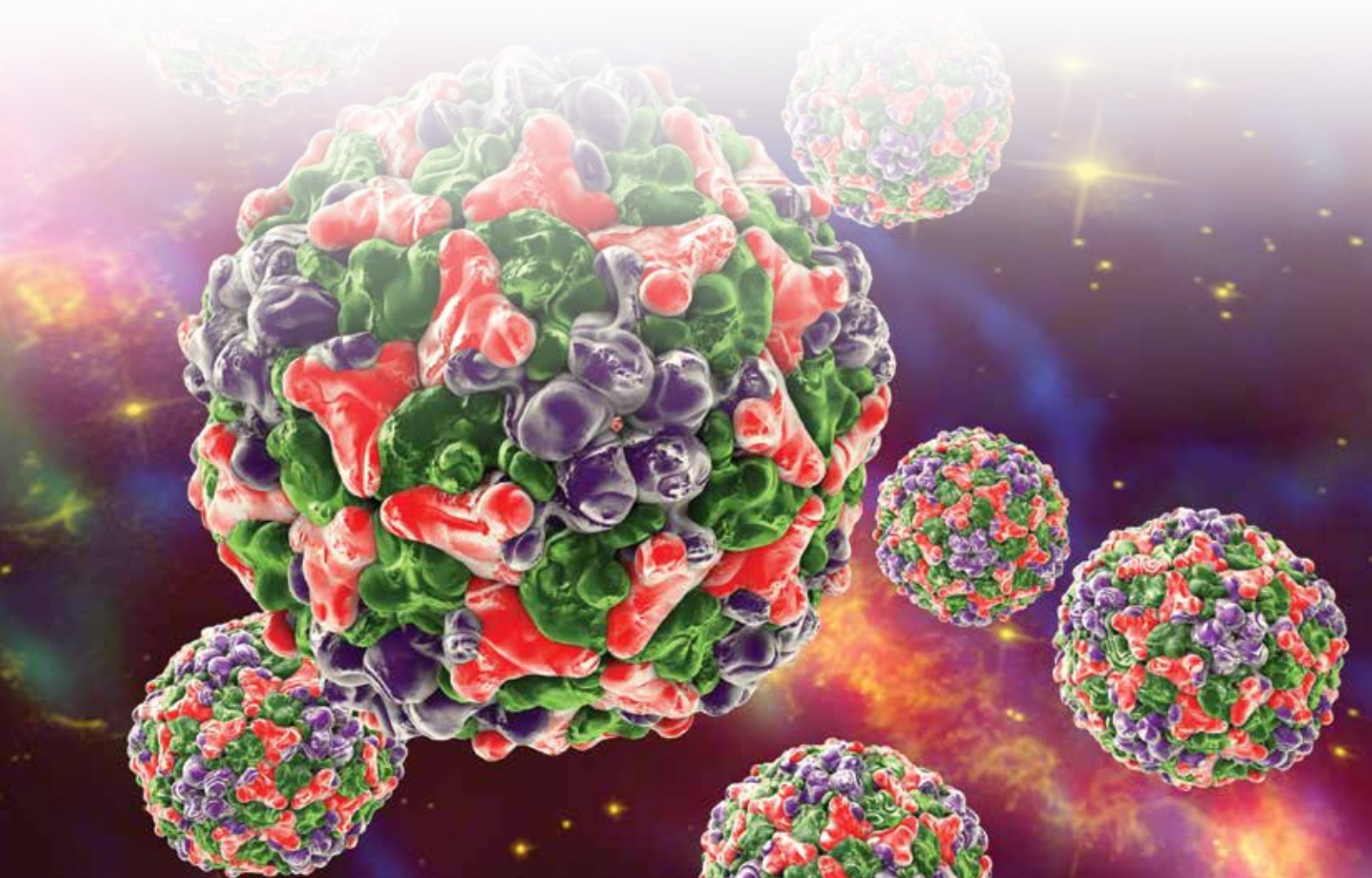
NHS Blood and Transplant

Blood and Transplant Matters

Information for hospitals served by NHS Blood and Transplant

Inside



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Next Edition

Issue 48 will feature articles on:

- London Platelet Audit
- Patient Blood Management Strategy
- Easy as ABC? - Producing 'A Manual for Blood Conservation'.

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

EDITORIAL

Welcome to Edition 47 of *Blood and Transplant Matters*, I hope you enjoyed the last edition.

This edition starts with Nicky Anderson and Sue Barnes dispelling a few myths about eligibility for blood donation, discussing some new Emerging Trends in Donor Deferrals. Some of those emerging trends, are lifestyle choices, some are infection. Among the infection include a re-visit to West Nile Virus and a look at Chikungunya Virus. Chikungunya Virus was first detected in 1952 in Africa following an outbreak in the Makonde Plateau – between Mozambique and Tanzania.

Since then Chikungunya fever has been identified in nearly 40 countries World Wide. The name seems to be derived from the Makonde verb Kungunya – meaning to dry up, or become contorted or specifically "that which bends up".

Immanuel Kant's thoughts are next discussed with Dale Gardiner and Charmaine Buss in relation to Deceased Organ and Tissue donation. An article that should ensure that a patient's wishes are followed when practical. There follows an interesting account, by Judith Seddon, of a personal experience of the Tissue Donation Process, as seen through the eyes of a partner. This is followed by John Armitage's article, outlining the Development of Eye Banking in the UK. Providing an excellent introduction to the basis of corneal anatomy and physiology and recent trends in corneal transplant techniques. Next, Andrew Bradley summarises the work that the newly funded National Institute for Health Research Blood and Transplant Research Unit in Organ Donation and Transplantation will be conducting in the next few years.

Ansar Mamood outlines the requirement for National Registries and describes the function of UK National Ligament Registry that was officially launched at the British Association for Surgery of the Knee Annual Meeting in March 2013.

The Regulatory World of Cell Therapies is described by Keith Smith, who, also, outlines why novel test systems will need to be developed to provide sufficient scientific evidence of safety and mode of action before clinical trial and subsequent routine treatment can be authorised.

The future work of the National Institute for Health Research of Blood and Transplant Research Unit in Stem Cells and Immuntherapies is outlined by Karl Peggs – CAR T therapies have nothing in common with Henry Ford's Model T cars, but may lead to the manufacturing of immunotherapies for malignant disorders.

As always there are both CPD questions based upon these articles with answers appearing in the next edition – and two interesting cases complete with suggested answers and references, which I hope are both interesting and informative.

Have a happy read. Any further comments should be sent to myself or my hard working Editorial Assistant Lynne Hodkin at blood&transplantmatters@nhsbt.nhs.uk.

We have had one comment regarding Issue 46.

"I've just had a very quick scan of the clinical case studies in the September 2015 edition (Issue 46) of Blood and Transplant Matters.

With regard to Patient 2 (page 28, answers page 30) there is a sort of enigma with question 2. I fully realise that the question posed is *"What phenotype blood would you select for transfusion?"*, and the answer given is *"R1R1, Fy(a-), K- blood should be selected for transfusion."*, and, technically, with the way the question is set, this is correct, however, I note that the patient is on Fludarabine. Now, the enigma comes with the fact that the question has not actually been asked as to whether, in addition, there would be any special needs, but this patient would require irradiated blood (as Fludarabine is a purine analogue), and I wonder why the fact that the patient is on Fludarabine was mentioned, if the need for irradiation was not required in the answer?"

Correct, further special needs would need to be considered and irradiated red cells would be required.

Many thanks for those comments.

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Blood Donation Mythbusters – Emerging Trends in Donor Deferrals

The eligibility criteria for blood and platelet donors are decided by the Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) and the full guidelines can be accessed at www.transfusionguidelines.org/dsg. They are based on the Blood Safety and Quality Regulations (SI 50, 2005) and the underlying EU directive.

These guidelines are regularly updated as new risks are identified to either donor health or patient safety. The aim of this article is to highlight some recent changes to the guidelines and to remind readers of the detail of some long-standing rules that are still applicable in a hospital setting.

I've been transfused – can I be a blood donor?

The UK does not accept donations from people who have had a transfusion anywhere in the world after January 1st 1980. This includes transfusion of red cells, platelets, fresh frozen plasma (FFP), cryoprecipitate, cryodepleted plasma, granulocytes, buffy coat preparations, and human normal immunoglobulin. There is a discretion to allow for specific immunoglobulin therapy for example anti-D. Also included in this definition are mothers whose babies have required intra-uterine transfusion of red cells or platelets and also any patient who has had a plasma exchange or who has received treatment with blood derived coagulation factor concentrates including prothrombin complex to reverse over-anticoagulation.

However, donors may be accepted after treatment with human specific immunoglobulin given as prophylaxis such as anti-D, tetanus or hepatitis immunoglobulin.

I've been travelling. When can I donate?

The commonest reasons for deferral after travel occur when the donor returns to the UK after visiting a country with endemic malaria. A straightforward visit to a malarial country requires a six month deferral and then a test for malarial antibodies if a donation is to be taken within 12 months of the donor's return to the UK.

People who have lived in a malarial country for more than six months at any time of life cannot donate for six months after their return to the UK and must have a test for malaria antibodies, no matter how long it is after their return. Donors who have had malaria must wait three years after their recovery and will then require a malaria antibody test.

Some donors who have travelled to Central or South America will be deferred for six months and will require a test for *Trypanosoma cruzi* (Chaga's disease or South American sleeping sickness). This is in addition to any test for malarial antibodies.

A donor who was born in Central or South America or whose mother was born there will also require a test.

There are a number of emerging infections worldwide that could be transmitted by blood transfusion. These include West Nile Virus (WNV) and Chikungunya (ChikV) Virus, Dengue Fever and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The spread of these viruses is carefully monitored and the eligibility criteria are modified as newly affected countries are identified.

West Nile Virus, which is transmitted by mosquitoes from birds to humans, is spreading across Europe from East to West. The USA and Canada are also affected. Donations from donors returning to the UK from affected areas between 1st May and 30th November are tested for WNV RNA.

There is a 28 day deferral for donors who have returned from countries with endemic ChikV or Dengue fever as long as the country does not also have malaria, in which case a six month deferral is applied.

The travel rules can be very complex and donors are encouraged to ring the donor helpline (0300 123 23 23) with the details of their travel to get accurate information about their eligibility before attending a donor session.

I've had a tattoo – when can I donate?

A donor must wait four months after a tattoo, Derma-rolling, ear and body piercing, or permanent and semi-permanent make-up. The donation must then have an additional test for the antibody to hepatitis B core antigen (anti-HBc) to exclude hepatitis B infection. During the recovery from a Hepatitis B viral infection, levels of free hepatitis B surface antigen (HBsAg) may be too low to detect and anti-HBc may be the only indicator of infectivity. If the anti-HBc test is positive, in other words, there is evidence of a naturally acquired hepatitis B infection, the donor also has to have anti-HBs measured at more than 100 iu/ml in order to continue to donate.

I've used some self- injected tanning agent – can I donate?

There has been a recent amendment to the blood safety entry in the donor selection guidelines which now permanently excludes anyone who has used body–building drugs and injectable self-tanning agents such as Melanotan. These preparations are unlicensed and are often obtained over the Internet with an uncertain provenance. Melanotan is believed to have serious side effects and there is a risk of needle sharing and sharing of the multi-dose vials that are supplied.

We encourage our donors to ring the National Donor Helpline: 0300 123 23 23 with any queries about their eligibility to donate in order to save a wasted journey to a donation session.

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References:

JPAC Transfusion guidelines;
http://www.transfusionguidelines.org/dsg

Blood Safety and Quality Regulations;
http://www.legislation.gov.uk/uksi/2005/50/pdfs/uksi_20050050_en.pdf

Donation is kantian not utilitarian

"So act that you use humanity, whether in your own person, or in the person of any other, always at the same time as an end, never merely as a means."

Immanuel Kant's second categorical imperative.

The German philosopher Immanuel Kant believed that no individual should be treated as a means to an end, but should be allowed to choose their own end (goal). This means that individuals should not be used without their consent and this is held true even if by doing so, another life may be saved. Whereas utilitarianism is often considered as the opposite philosophical view, that it is the consequences that matters and the right moral action is the one that leads to the greatest amount of happiness (good) for the greatest number of people.

So where does blood, organ and tissue donation fit into this philosophical mix?

For blood and living organ donation there is recognition, especially in how it is promoted in the NHS and portrayed in the media, that the donation is voluntary in nature and driven by the good will of the individual donating. A philosophical alignment therefore that is broadly kantian. This is not withstanding the fact that many living organ donors are in a familial relationship with the intended recipient of his or her organ. Familial obligations make gift giving complex (as most of us are reminded each Christmas season) but do not remove the choice that an individual must make, to give or not to give. Living organ donation even requires an individual to make an active choice to accept the risks to their own health and make donation a personal goal (end).

Traditionally deceased organ and tissue donation has been justified and promoted with more utilitarian arguments that focus on recipient need and outcomes. From the earliest history of transplantation to the near present, the human narrative has been about the tragedy of the transplant waiting list and the miraculousness of medicine; where the cult of the surgeon has loomed large.

But there has been a wind of change. A change that has swept right across the legal, ethical and professional framework that deceased donation rests upon. A change that has led to a massive cultural change in UK intensive care units and a sixty percent increase in deceased organ donation. And that change says – it all begins with an individual at the end of life - and what counts is acting according to the values, wishes and beliefs of that individual. It is only if that individual wished to be a 'donator' that the processes required to realise deceased donation, can be justified. This is a kantian claim.

What helped drive that change was the realisation that deceased donation is the most complex medical activity the NHS ever does in any twenty-four hour period. Such a period of activity cannot simply be reduced to a binary yes or no; organ available or not available. The strength of a wish to donate is a key determiner to what is legal and ethical in deceased donation. Once again this is kantian.

All four UK governments have published legal guidance to guide clinical staff involved with deceased organ donation after circulatory death (DCD). Importantly the decisions and interventions involved in DCD have to begin on living patients who lack capacity, in the hours before death; not deceased patients. As such the deceased donation legislation in the UK, the various human tissue acts, which set out the legislative requirements for seeking consent and authorisation to deceased donation, are not applicable as guides for clinicians while the patient is still alive. Instead, the legal guidance justified procedures to facilitate DCD by making reference to other non-donation

legislation, which is used to guide clinicians in caring for patients without the capacity to make decisions for themselves: Adults with Incapacity (Scotland) Act 2000 and the Mental Capacity Act 2005. The acts, their associated codes of practice and previous case law, make it very clear in the UK that the present and past wishes and feelings of the adult with incapacity should be accounted for, including seeking the views of the nearest relative and the primary carer of the adult, when deciding if an intervention is of benefit.

"Once it has been established that a person wanted to donate, either through direct knowledge of their wishes or as a result of discussions about what the person would have wanted, successful donation may be seen to be in the person's wider best interests."[1]

More recently the independent UK Donation Ethics Committee (UK DEC) has published generic guidance on decision making for interventions required before death to optimise donor organ quality and improve transplant outcomes.[2] UK DEC describes a decision making process that requires an assessment of the balance of benefits and harms for any such intervention; and that the strength of the patient's decision or wish to donate plays an essential role. Note how in both the legal and ethical guidance what justifies the actions required for optimising organ quality is not referenced to the recipient but the donor.

A wish at the end of life however is no magic wish, a kantian trump card. Were a family to say that their dying relative wished to be placed in a rocket after death and launched at the moon, doctors and nurses would probably endeavor to do so – but only if this was something society was willing to pay for. It is because of the benefits to recipients that society pays for organ donation. Striking a balance between kantian and utilitarian philosophies are where true protections for both the donor and the recipient are found.

Does the introduction of deemed consent in Wales alter this balance? From December 2015, Welsh residents, who die in Wales, if they have not indicated a wish not to donate in life (for example recorded this wish on the NHS Organ Donor Register), their consent for donation will be deemed. Traditionally this is regarded as a utilitarian method of promoting organ donation. Yet when the legislation was debated by the politicians and in the media, a key point that was emphasised, was how survey after survey reveals that the UK population supports organ donation. Were this not to be the case, it seems unlikely the legislation would have been passed. So kantian philosophy can be seen operating even within what, at first glance, seems a utilitarian initiative.

In the end, blood, organ and tissue donation policy, like nearly every other societal arrangement, is ethical when it achieves a satisfactory balance between kantian (individual's rights to choose) and utility (societal justifications).

Some of you may have watched the ITV special in 2013 where Will Pope (a heart transplant recipient) met Steve Ince, the father of Tom, Will's donor. Steve's words capture better than any philosopher what donation and transplantation is all about:

"It would have been easier, if I am honest, to say no. It would have been much easier to say, 'No leave him alone he has been through enough. I don't want you to touch him.' But that wasn't Tom's wish. That was just me as a father trying to protect him. But realistically you are not really protecting him you are just hindering his wishes and so if we would have wavered, there would be people who wouldn't be alive today."

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References:

1. Department of Health (UK), *Legal issues relevant to non-heartbeating organ donation* (2009).
2. UK Donation Ethics Committee, *Interventions before death to optimise donor organ quality and improve transplant outcomes: guidance from the UK Donation Ethics Committee* (2014).

Disclaimer

The views expressed are of those of the authors and should not be interpreted as reflecting the views of NHSBT or the Welsh Government.

My Experience of Tissue Donation – Judith's Story

When I was little my dad used to carry a Kidney Donor Card in his wallet and I remember many, many conversations about this card. I remember my dad explaining what it meant, especially the bit where it stated that he had discussed his wishes with his next of kin. I could not wait until I was old enough to have a donor card of my own and when I was 18, I got one.

When I was about 15 my brother played for Aspull Rugby Club and I helped out serving Pie and Peas on match days. It was there that I met Keith, (he was a volunteer with St John's Ambulance and did First Aid on match days as well as "injury repairs") at the club the following week. I remained involved with the club for quite a few years and did a project for my Human Biology A' Level on position related injuries. Keith and I then went our separate ways.

I trained as a nurse in the early 1980's and when I qualified, I worked in theatre, on Coronary Care, Intensive Care and Coronary Aftercare. I remember having a patient who was not going to recover and their family had made the decision to allow donation. People were very mindful of supporting the relatives, but what has always stayed with me was the reverence that the patient and their family received from all the staff.

We couldn't really do very much to help any of them other than to look after them, be there with them and show that we cared. It was hard when the patient went to theatre for the procedures knowing that they were not going to be coming back. The family and staff said their goodbyes, but knowing that there was something good going to come out of that tragic situation helped just a little bit.

I then did Agency Nursing for a while after I had my first son. When I became pregnant with my second son, I had a career break from nursing and after a few years, I re-trained as a counsellor and got a job working with Social Services in 1999 as a Counselling Co-Ordinator, I also got divorced and moved back "home" to Wigan.

I attended a function on 2nd April 2011 and part way through the evening was once again introduced to the aforementioned Keith. Now, given that it had been approximately thirty years since I last saw him, he was out of context, gone were all identifying features such as his St John's Ambulance Uniform, First Aid Box, Eau de Wintergreen, thick blond hair and lean physique … surely I could be forgiven for not immediately placing him.

We started "Courting" and in December 2013, we got engaged and the wedding was set for 25th October 2014.

On 1st August I finished work for the weekend and made some final preparations for our weekend. The whole family went to Cheltenham early on the Saturday for my sister in law's wedding we had a wonderful, very happy day. We arrived home late that night.

On the Sunday morning Keith got up and made the brews and we stayed in bed talking about the previous day. At 11 am Keith said he felt a bit odd and as I was looking in his eyes, I saw something happen. I did his blood pressure, which was very high and I wondered whether he was dehydrated from the day before so I encouraged him to sip some water but I stayed with him while he rested. I continued to monitor his BP for the next 40 minutes. At first it came down, and then it shot back up. I was just having the debate with myself about calling an ambulance/ going to the walk-in/or to leave it a bit longer when Keith had a fit. The decision was made for me.

I rang 999, asked for an ambulance and called my eldest son. I issued instructions to my son about the dogs, for him to wait on the front for the paramedic and then the ambulance and I continued on the call with the operator. The fit lasted maybe two or three minutes but from 11.40am time had no real significance anymore. The crews arrived and Keith with help, was able to get dressed and get in the ambu chair.

We got to Wigan Infirmary at 12.30hrs and Keith was examined very quickly and was sent for a scan. I waited outside the scanner room and heard a female voice asking Keith to relax and stay still. I then heard her ask for a doctor in a voice that was about twenty octaves higher than the first one.

Medical and Nursing Staff were flying into the room with equipment and then one of the porters came out and very kindly asked me to move away from the door

to somewhere quieter where I could sit down. I fully understood what he was trying to do and I greatly appreciated his kindness, concern and desire to look after me but there was no chance that I was going anywhere. A nurse came out of the room and explained to me that Keith was very unwell and they were working hard to stabilise him.

A short while later a Doctor came out to speak to me, he explained that they had sedated Keith and done the scan but that there was extensive bleeding on his brain and it wasn't looking good. He told me that they would be sending the images to Hope Hospital for review by one of the Neuro specialists there but that I should prepare myself because the damage was so great that it was unlikely that Keith would survive.

I think, but I can't be sure that he mentioned the possibility of donation at this point. He also said, that he had been informed of my request to be admitted to the room should it become apparent that Keith's life was unsustainable. I consider myself to be intelligent, articulate and sensitive, but in those moments "brain freeze" took on a whole new meaning. Words didn't make sense, I could not process what was happening and I certainly couldn't think straight.

Keith was moved back to Resus in A&E and it was on this journey that I realised that I was going to need the support of my family. I went outside and rang my mum who dispatched runners to the golf course to inform my dad, arranged for my eldest son to pick her up and come to be with me. Keith was still ventilated at this point and in an induced coma. My mum, son and his girlfriend arrived and were shown in.

I then remember two of the A & E Nurses asking to speak to me in the Relatives Room. Having been a nurse, I knew this was going to be a "Dead Man Walking" conversation, so mum and I went through. I knew one of the nurses from another part of my life and the other was the one I had spoken to outside the Scan Room. I trusted both of them. We had a bit of a chat and they asked what my understanding of the situation was. I answered and they then asked me about donation. The subject was broached sensitively and I had every opportunity to ask questions and have time to think about it, I didn't feel rushed or pressured.

I remember saying that organs were probably not an option for donation because Keith had had an "event", had COPD and there were other reasons why his organs would not be viable. At this point, despite my training and clinical knowledge, I was not fully aware what other ***opportunities*** for donation may be available. I remember saying that as far as I was concerned anything that could be salvaged from such a horrible situation would be a bonus, but that Keith's blood family would need to have the final say and that if they had any objections then donation would not be possible.

For me, this was one of those times when I had to TOTALLY rely on other people.

- I was not functioning as a sentient human being.
- I felt unable to initiate any thoughts.
- I could not process any logical thoughts or information.
- I could not think ahead.
- I could not think full stop.
- In three hours **my** world, **my** life and **my** future had changed beyond anything **I** could have envisaged.
- I would say that I was probably **the** most vulnerable that I have ever been in my life.

For me, this is where it was **SO** important that those Nurses talked to me about the possibility of donation.

I received a phone call from Leanne who works for NHS Tissue Donation. She explained that she had been given my details from the staff at the hospital and was calling to speak to me about the possibility of donating some of Keith's tissues. Leanne explained that they may be able to use Keith's eyes, skin from his back and legs and bone from his legs, she told me that there was a purpose built facility in Speke, Liverpool where the procedure could take place or it could be done at the hospital and Keith would be treated with the greatest respect. Leanne explained about the time frames for donating tissue and that it was critical that eyes would need to be removed within 24 hours of a person's death, she also said that the Coroner would be involved and he may want to speak to me to ensure that this was an informed decision.

Leanne told me that there may be a little bruising around Keith's eyes after the procedure and that due to there being no bone in, or skin on Keith's legs I would need to give consideration to what he wore. I have to say, this made me smile; I am not sure what Leanne pictured Keith wearing but he was 6'3", VERY well fed and NEVER to my knowledge wore a mini skirt!

Due to the timings, it looked like Keith would have to stay at Speke overnight. I asked Leanne whether he would be in a Chapel of Rest or a Mortuary overnight and she told me it would be a Mortuary. I have NO idea why this was important to me, because had Keith still been at the hospital he would have been in a Mortuary. There was NO logic in my thinking at all, but I got really hung up about it and thanks to Leanne's great perception, she recognised my distress and suggested they come to Wigan to do the procedures.

Leanne told me that it would be possible for me to be notified around the time of Keith's first anniversary what had been transplanted or used. I could opt in or out of this, I opted in.

So, the procedure went ahead and Keith did have a tiny bit of bruising to one eye but apart from that, there were no other visible signs that anything had taken place.

So, a year on I found out that the cornea's from Keith's eyes had been transplanted into a 26 year old male and a 32 year old female.

Keith's bone had been used in six procedures to date such as hip and knee replacements. What better legacy can any of us leave than to give another human being the chance to see again or to be able to walk properly or to be free from pain?

- I would like to emphasise the comfort that I and those who loved Keith took from knowing how he had helped people. This was more poignant for me because I have a friend who has no sight and when I told her about the two people who had benefited from Keith's corneas she said "if only". This REALLY slammed home the personal message to me.
- My son had a friend who was in his early twenties called Michael. Michael died eleven and a half months ago in Birmingham Hospital waiting for a heart and lung transplant. Michael's family donated his eyes for transplant. Michael wasn't able to benefit from donation but that didn't stop him wanting to help others.
- For me, it is vital to register your agreement for donation regardless of your age.
- It is also vital to talk to your loved ones about donation, however difficult this is and to be mindful to and respectful of each other's wishes. Some people may not want to donate. Some people may only want to donate specific parts. Some people may want to donate everything.
- What is crucial is that we all talk about it whether you are in a personal or a professional capacity.

Judith Seddon

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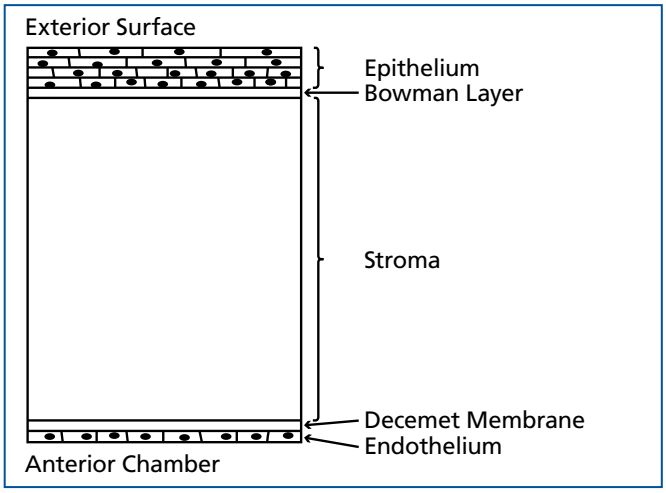
Development of Eye Banking in the UK

The cornea is a little over 0.5 mm thick and consists of five layers: an outer stratified epithelium, 5-7 cells thick; Bowman layer; the collagenous stroma, which makes up 90% of corneal thickness; Descemet membrane; and a monolayer of non-proliferating endothelial cells lining the inner corneal surface (Figure. 1). It is the major refractive component of the eye and good vision requires a clear cornea with a smooth, spherical shape. Corneas transmit up to 95% of light in the visible spectrum with minimal scattering. This transparency critically depends on the regular arrangement and uniformity of the collagen fibrils embedded in the proteoglycan matrix of the corneal stroma. This arrangement in turn relies on the active control of stromal hydration by energy-dependent ion pumping mechanisms of the corneal endothelium.

Endothelial dysfunction caused by disease (for example, Fuchs endothelial dystrophy) or surgical trauma (for example, pseudophakic bullous keratopathy) can lead to loss of transparency and severe visual impairment. Other important causes of sight loss include stromal thinning with distortion of corneal shape (keratoconus) and infections such as herpes keratitis. For many of these patients with cloudy or misshapen corneas, vision can be restored by a corneal transplant.

Figure 1: A representation (not to scale) of a transverse section of human cornea.



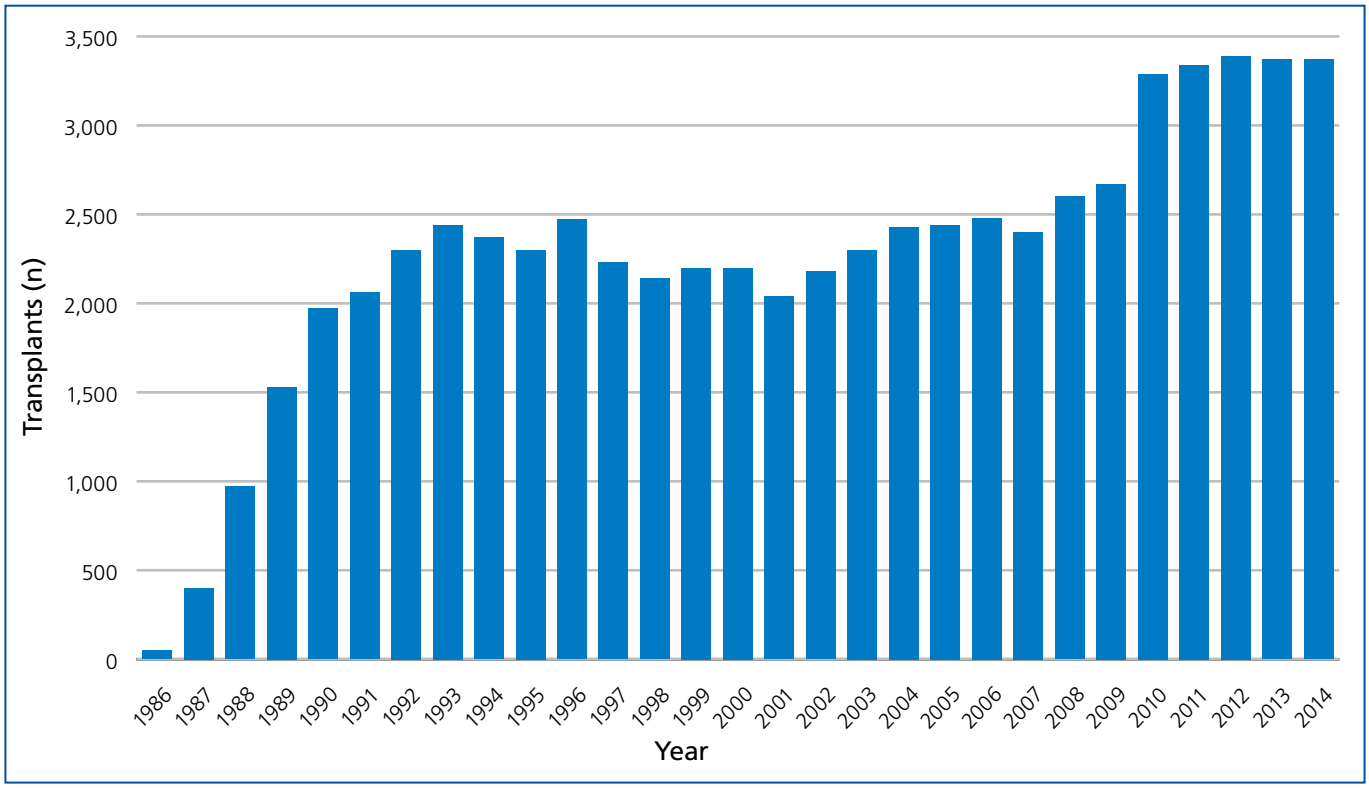
The first successful corneal transplant was reported by Zirm in 1906[1] and the first transplant in the UK was carried out in 1930 by Tudor Thomas at Guy's Hospital. Owing to the perception that tissue from a deceased donor would be toxic, the corneas for these early transplants came from living donors who had undergone therapeutic enucleations. Also, at least in the UK, there were legal barriers: the removal of 'fresh' tissues from the deceased was illegal under the Anatomy Act 1832, which was enacted to curtail the activities of the 'Resurrectionists'.

However, in the 1930s, Filatov, a Russian surgeon, not only pioneered the use of corneas from deceased donors but advocated the storage of whole eyes in glass jars ('moist chambers') in ice for several days. The first eye bank was opened in New York in 1944. In the UK, the Corneal Grafting Act 1952 permitted the removal of 'bequeathed' eyes from deceased donors and this led to the setting up of the first UK eye bank at the Queen Victoria Hospital, East Grinstead. This was followed in 1967 by the eye bank at Moorfields Eye Hospital in London. The Human Tissue Act 1961 allowed registered medical practitioners to remove tissues and organs from the deceased for the purposes of transplantation. This was amended in 1986 to allow non-medics to remove eyes from donors.

With the establishment of eye banks, better ways of storing corneas were developed. Corneas stored as whole eyes in moist chambers had to be transplanted within 24-48 hours of the donor's death. The removal of the cornea with a rim of sclera (a corneoscleral disc) and storage in tissue culture medium at 4°C was popularized in the 1970s.[2] This increased storage time to several days. With further developments in the 1990s,[3] the hypothermic storage time was increased to two weeks: this is the method used by US eye banks.

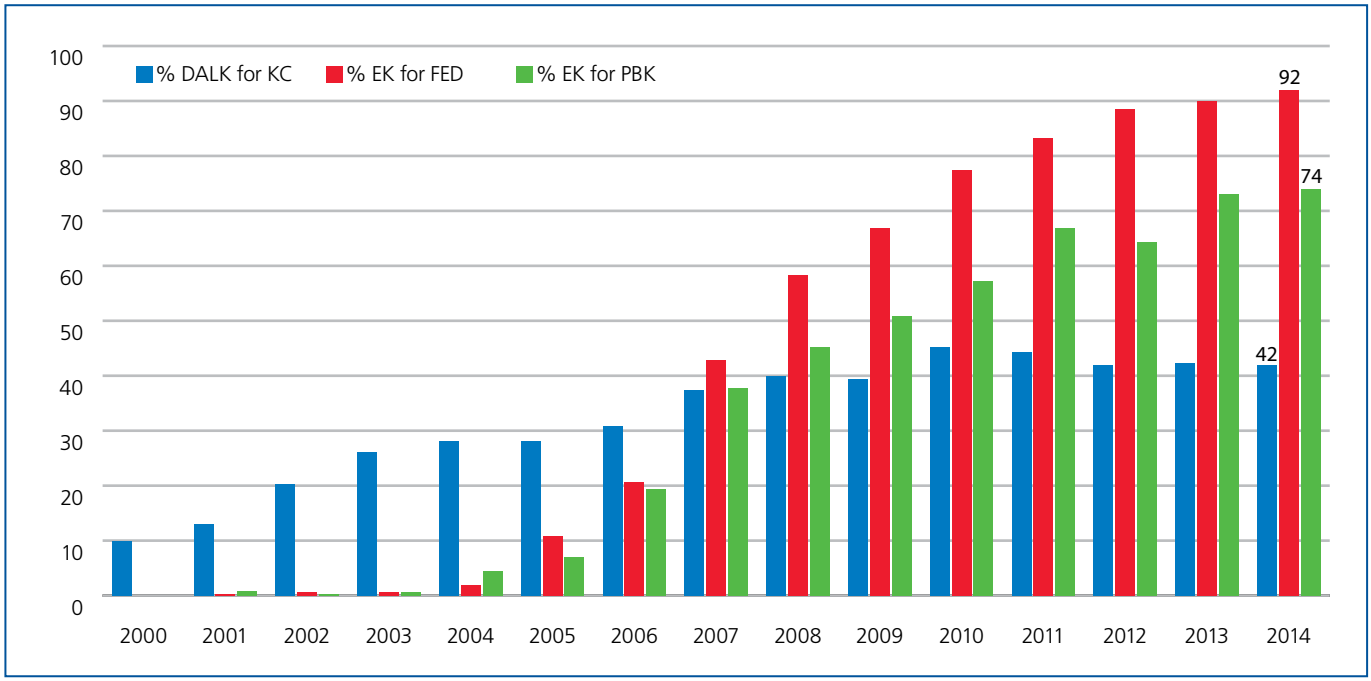
An alternative storage method, organ culture, was also developed in the 1970s. Corneoscleral discs were stored in tissue culture medium at 31-37°C. This extended the storage period to four weeks compared with, at the time, just a few days with hypothermic storage. After refinement of the technique by eye banks in Denmark and Amsterdam,[4] this was the method adopted when setting up the Bristol Eye Bank, which issued the first organ-cultured corneas for transplantation in the UK in March 1986. Organ culture has since become the method of choice for the majority of European eye banks. Bristol Eye Bank was set up by Bristol University in collaboration with the former UK Transplant Service (UKTS). The Corneal Transplant Service (CTS), launched in October 1983, established a national distribution service for corneas similar to that provided by UKTS for organs. Coupled with extended organ-culture storage, this service transformed corneal transplantation from an out-of-hours operation arranged at short notice and dependent on the availability of local eye donors to an elective procedure that could be planned well in advance. Also, corneas were always available for clinically urgent transplants anywhere in the country.[5] Manchester Eye Bank became part of the CTS in 1989. Between 1986 and 2014, almost 66,000 transplants were performed with corneas provided by this service (Figure. 2) and, currently, there are 3,500 corneal transplants a year in the UK. The eye banks also supply sclera for reconstructive and glaucoma surgery and are important providers of ocular tissue for surgical training and research into the causes and treatment of eye disease.

Figure 2: Corneal transplants supplied through NHS Blood and Transplant



Over the last 10-15 years there has been a marked change in transplant techniques away from replacing the full thickness of the cornea (penetrating keratoplasty, PK) to replacing only those parts of the cornea that are dysfunctional (Figure. 3). In endothelial keratoplasty (EK), the corneal endothelium on its basal lamina (Descemet membrane) with or without a thin layer of stroma is inserted into the anterior chamber of the eye through a small incision in the sclera. The advantages of this technique are faster visual rehabilitation, lack of sutures and maintenance of corneal nerves. For keratoconus and stromal scars, deep anterior lamellar keratoplasty (DALK) replaces the full thickness of the stroma, leaving the patient's endothelium intact.

Figure 3: By 2014, 92% of transplants for Fuchs endothelial dystrophy (FED) and 74% for pseudophakic bullous keratopathy (PBK) were endothelial keratoplasty (EK), and 42% for keratoconus (KC) were deep anterior lamellar keratoplasty (DALK), demonstrating the move away from full-thickness to partial-thickness (lamellar) grafts to replace only the dysfunctional part of the cornea.



All corneal transplants are followed for five years and outcome data (survival, complications, and visual outcome) submitted to the UK Transplant Registry, which also holds organ transplant outcome data. This has allowed not just the monitoring of national activity data but has enabled a large number of studies to be undertaken to improve our understanding of the factors that influence graft outcome. This has been especially important for evaluating the outcomes of the new lamellar techniques. Registry data have also been invaluable for validating the quality and safety of corneas stored and assessed by the Bristol and Manchester eye banks both in terms of suitability for transplant and graft survival.[6]

Eye banks are regulated by the Human Tissue Authority under the Human Tissue (Quality and Safety for Human Application) Regulations 2007. Government and professional advice and guidance are also followed, and the European Eye Bank Association (www.europeaneyebanks.org) provides a clinical and scientific forum for European eye banks.

Ten years ago, UK Transplant merged with the National Blood Service to form NHS Blood and Transplant (NHSBT). More recently, on 1 April 2015, the Bristol and Manchester eye banks transferred to NHSBT Tissue and Eye Services (TES). This now means that NHSBT manages the complete supply chain for ocular tissue from eye donors through to the provision of tissue for transplant patients. Moreover, possibilities for the development of new services for surgeons have opened up; for example, Manchester Eye Bank recently began 'pre-cutting' corneas for endothelial keratoplasty. With wider access to research and development and greater integration with other specialist areas of TES, there is now a firm foundation for the further development of eye banking in the UK for the benefit of surgeons and their patients.

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The National Institute for Health Research Blood and Transplant Research Unit (BTRU) in Organ Donation and Transplantation

We are delighted to report that this new Unit opened on October 1st 2015 and will receive a total of £3.8M of funding from the National Institute for Health Research (NIHR) over the next five years to support key staff, trainees and consumables. The Blood and Transplant Research Unit (BTRU) is a strategic partnership between the Universities of Cambridge and Newcastle, and their associated transplant units, and NHS Blood and Transplant (NHSBT). The overarching aim of the BTRU is to develop and evaluate novel approaches and technologies that will increase the availability of suitable donor organs for transplantation, while improving graft survival. To help achieve this we are strengthening existing links and building new collaborations between leading scientists and clinicians to create a BTRU that attracts the best young doctors and scientists and helps them develop into the future researchers in transplantation.

The focus of our BTRU is on the clinical pathway from identification of a potential deceased organ donor to the implantation of the donor organ into the most appropriate recipient. We chose not to focus on subsequent management of established transplant recipients since, in both Cambridge and Newcastle, research programmes aimed at improving transplant outcomes by better recipient management are already well-established and will add to the scope of the BTRU.

Our BTRU has four key objectives. The first of these is to improve organ donor management and evaluate novel interventions in deceased donors. The overall aim here is to increase the number and improve the quality of transplantable organs from deceased donors, in line with the NHSBT Transplantation vision. A particular focus is on improved management of donation after circulatory death (DCD) donors, since these comprise almost half of all deceased donors, but yield significantly fewer transplantable organs than donation after brain death (DBD) donors. We want to develop novel algorithms that allow prediction of time to death after withdrawal of life supporting treatment, and to better understand the impact on organ donor quality of functional warm ischaemic time in other words, the time during the agonal period prior to cardiorespiratory arrest when organs are inadequately perfused with oxygenated blood. The safety, practicality and efficacy of in situ normothermic regional perfusion (NRP) of abdominal organs in DCD donors is being evaluated. This technique involves, after verification of death, cannulating the aorta and vena cava and then connecting an extracorporeal circuit that warms and oxygenates donor blood before returning it to the donor, typically continuing for a period of around two hours before organ procurement. NRP allows assessment of organ function in situ and has the potential to improve transplant outcomes. We also plan to assess the feasibility of normothermic antegrade perfusion of hearts in DCD donors.

Our second key objective is to develop novel approaches for assessing donor thoracic and abdominal organ quality. We are developing a comprehensive approach based on histological analysis, analysis of mitochondrial function, genetic profiling, analysis of putative biomarkers in blood, urine and tissues, and in situ functional assessment of organs prior to retrieval. We anticipate this will allow identification of organs that might previously have been discarded to be transplanted safely into recipients. It might also allow risk stratification of transplantable organs and identify those organs in need of interventional rescue therapy prior to transplantation.

Our third key objective is to evaluate normothermic ex vivo perfusion as an approach for resuscitating and reconditioning thoracic organs and kidneys that have been removed from the donor. Both Cambridge and Newcastle have particular expertise in this area and ex vivo perfusion is a major underpinning technology within the BTRU. The focus here is on organs that are currently deemed sub-optimal and give inferior outcomes if transplanted, or are deemed unsuitable for transplantation and discarded. Our hypothesis is that such organs can be resuscitated and reconditioned by ex vivo perfusion. Essentially donor organs are perfused for a period of time with warm oxygenated solutions that allow restoration of function in the absence of potentially harmful leukocytes and inflammatory mediators, before transplantation into the hostile inflammatory environment of the recipient. Ex vivo perfusion allows the function of donor organs to be assessed by a wide range of methods. Importantly, it also provides an opportunity for delivering and evaluating novel therapeutic interventions to improve donor organ quality. Our hope is that organs that might otherwise have been discarded will be identified as suitable for transplantation and that new interventions will be discovered that recondition sub-optimal donor organs and prevent further tissue injury.

Our fourth objective is to reduce the demand for re-transplantation through improved understanding of donor/recipient compatibility and the use of novel interventions to protect and improve long-term graft function. Under this objective we are using recent advances in computational molecular modelling techniques and detailed information

from X-ray crystallography to investigate Human Leukocyte Antigen structure and matching. We are also determining the impact of killer-cell immunoglobulin-like receptors (KIR) on kidney, liver and lung transplant outcomes using a rapid KIR typing system. The relationship between markers of biological age and graft function is also being examined as an approach for stratifying risk matching between donor and recipient.

While pursuing the above research objectives, the ambition of the BTRU is to develop a comprehensive research platform that facilitates rapid translation of new developments in transplantation and their implementation into clinical practice through a productive partnership with NHSBT. Our aim is to offer high quality training opportunities to medically qualified researchers, scientists and other professional groups allied to medicine to improve expertise and capability in translational research studies and applied health research in transplantation and to deliver a new generation of transplant researchers to the UK. Involving and engaging the public is central to the mission of the BTRU; we have a comprehensive strategy for achieving this and are working in close partnership with the NHSBT communications and external affairs team.

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UK National Ligament Registry (NLR): An Effective and User-friendly Mechanism to Assess Clinical Outcomes?

National Registries are becoming increasingly important and produce demographic and outcome data of interest to patients, surgeons, industry, insurers and National health systems alike. This outcome data is generally in the public domain and therefore must be valid and robust. The UK National Ligament Registry (NLR) is designed to collect and store outcomes data relating to knee anterior cruciate ligament (ACL) reconstruction surgery. It was officially launched at the British Association for Surgery of the Knee (BASK) annual meeting in March 2013, with the backing and support of the Executive and members. The main objective of the registry is to provide data to enable surgeons to understand the outcome of ACL reconstruction surgery. Analysis will identify revision rates, evaluate functional outcome on patient reported measures and identify current and emerging trends in practice. Resulting targeted research can be designed to improve the outcomes for patients.

Data Collection Method:

The Registry platform is easily accessible via computer or tablet, and can be used via a smart-phone, simplifying the process of data entry for clinicians and patients. The 'registry route' is simple, requiring small contributions from both surgeon and patient at different stages. It also automatically prompts patients to fill in their information at scheduled times of treatment and rehabilitation, taking the hassle and stress out of clinical data collection for clinicians.

In overview the data collection process is as follows:

1. When ACL reconstruction surgery is planned patients are registered on the program
2. Patients receive an email link to securely enter details of their injury, sporting function, and some baseline functional scores. Alternatively data is collected on a computer/tablet on admission to hospital
3. Surgeons log-on after completion of surgery and enter the operative data
4. The program then emails the patient at various scheduled stages, prompting them to enter information for several validated outcome scores.

Current Status:

The first annual report was released in March 2015 at the annual BASK conference, and includes data from 2854 patients under going primary ACL procedures between December 2012 and February 2015. There is data from over 150 surgeons in the database, and more than 220 surgeons have registered. The use and input is currently voluntary and growing as the message of the registry spreads. The ability for the system to provide reports for revalidation and annual appraisal, in addition to detailed analysis of outcome widens the appeal.

Allograft tissue is an important option for graft choice, especially in revision ACL surgery. This is reflected in the report where autograft was the most common graft choice for ACL reconstruction procedures (98.5%). Allograft was used in primary ACL reconstruction surgery in 1% (n = 20) of the patients from a total data set of 2011 patients where

the type of graft was specifically recorded. Synthetic graft was used in six patients only. When the ligament registry is expanded to record revision ACL surgery important data relating to utilization of allografts will increase. This is particularly important as revision ACL surgery grows in frequency and data on treatment options is essential.

NHS Blood and Transplant Collaboration with NLR:

When collecting clinical follow up, it is vital to work closely with the clinicians who use the grafts. To accomplish this, NHS Blood and Transplant Tissue Services' (NHSBT TS) strategy has been to establish clinical liaison groups with surgeons through their professional societies. Working with BASK, NHSBT TS initiated collection of clinical follow up data for tendon allografts between 2008-2011. Reports of graft use were made by individual surgeons to NHSBT, who then took responsibility for contacting the patients directly at the designated follow up points to gather data on patient reported outcomes. In this study, an initial notification rate of 35% of issued grafts was obtained over a three year period concluding in September 2011. This translated to 128 patients. At the 12 month follow up stage, a response rate of 47% was obtained, equivalent to 10% of the grafts issued during the study period. Data collection proved cumbersome and it was recognized that the paper system at that time was not sufficiently robust to provide meaningful results.

The new web based NLR system should overcome that hurdle. It is clinicial led and independent from central government. Stakeholders are provided with outcome data that will inform clinical protocols, funding providers, research, future device developments and ensure the best use of donated allografts.

Summary:

The UK National Ligament Registry has been designed by surgeons for the benefit of patients. It is an exciting collaborative project to enhance understanding and outcome following anterior cruciate ligament injuries.

The registry is accessed through the website www.uknlr.co.uk which contains background information, surgeon registration details and also serves as a large resource area for patients understanding the operation and rehabilitation. It is important that all knee surgeons contribute data to the NLR to build up an evidence base to inform best practice. The aim of the NLR steering group is to make it the 'go to place' for patients and also for medical or rehabilitation providers involved in knee ligament injury.

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Cell Therapies and Their Regulation

Recent advances in genetics, molecular biology and cell biology have created a new area of biotechnology whereby human cells can be manipulated in the laboratory either to modify their behaviour, or to make them differentiate and grow in cell culture allowing them to be used to treat disease where simple transfusion or transplantation of cells and tissue is not effective or possible. Products derived in this way may be known generically as cell therapies to distinguish them from transplants.

Examples of cell therapies currently fall into two categories, immunotherapeutic cells and regenerative cells. The first generation of cell therapy products, Chimeric Antigen Receptor T (CAR-T) Cell and Dendritic Cell therapies are examples of immunotherapeutic cells

and products that are already available or in advanced development for treating leukaemias, melanoma and prostate cancer. Regenerative cells are loosely known as "Stem Cells". Stem cells are capable of differentiating into a variety of cell types with the potential to regenerate whole tissues. Adult derived stem cells are restricted regarding their potential to differentiate and pleuripotent stem cells able to differentiate into most cell types are only found naturally in the early embryo. However, clinical trials have already been conducted to study the regeneration of cartilage using bone marrow derived stem cells and of ocular tissue using embryonic stem cells.

From a regulatory point of view, all cells to be used in the treatment of patients must be procured by an "Establishment" authorised by a "Competent Authority" in accordance with either the European Blood Directive or the European Tissue and Cells Directive (EUTCD). The former applies exclusively to blood to be used for transfusion, while the latter applies to all other uses for tissues and cells. Procurement in this context covers consent, donor medical screening for acceptability and the act of collecting a tissue or cell donation. The associated regulations lay down the minimal donor testing requirements which must also be performed under the direction of a licensed "Establishment". It is not legal to procure tissues or cells for patient treatment without a Licence unless they are procured from the patient and used for their own treatment during a single operation for example. autologous skin grafting for burns. In the UK the Competent Authority under the EUTCD is the Human Tissue Authority (HTA).

From this point onwards it becomes complicated, but basically if the product is going to be used to perform the same function in the recipient as in the donor this is considered as a transplant and the processing, storage and distribution remains regulated by the EUTCD. So, donated bone marrow used to regenerate the bone marrow of a patient following ablation therapy is a transplant but, bone marrow injected into heart muscle or knee joints to aid repair of damaged tissue is a regenerative cell therapy. Similarly, cells selected for their existing affinity for a particular immune target and isolated and used to act upon that target are considered transplants but, immune cells that are manipulated in cell culture to develop an affinity for a specific immune target are an immune cell therapy.

In the EU, such cell therapy products are classified as Medicines. So once the donated starting material for these products has been procured and tested in accordance with the EUTCD, new regulations apply and the processing of the cells into the cell therapy product is considered as pharmaceutical manufacture. The relevant EU Medicinal Product Directives and associated regulations provide very tight regulatory control that requires developers and manufacturers to scientifically demonstrate that the product is safe and efficacious.

The regulators of all cell-based therapeutic products expect the developer to identify the possible hazards to the recipient, to assess the associated risks and to mitigate the risks through controls over the manufacturing process and relevant testing of materials and product. For transplants the principle risks are well established and the blood, tissue and cell regulations and associated standards helpfully provide mandatory and guideline risk mitigation measures that must be implemented by Establishments and enforced by the regulators. However, once the cells are manipulated in vitro to direct their growth and development and their mode of action, a whole new series of potential hazards emerge. These are mostly related to possible genetic changes that can take place during cell expansion and differentiation in culture. Such changes may alter the immunological, or the growth and differentiation characteristics of the cells with the potential for serious adverse reactions or tumour formation in the recipient. It is not possible to conduct a clinical trial of the product until the regulator is satisfied that the developer has sufficient understanding and control over the quality and safety characteristics of the product, its mode of action and of the process of manufacture. Often this will require novel test systems to be developed to provide sufficient scientific evidence of safety and mode of action before a clinical trial and subsequent routine treatment will be authorised. This is one of the principle challenges for developers of these products.

Finally, like all biological products the quality of cell therapy products is inextricably linked to their manufacturing process. Therefore, all the manufacturing variables such as media ingredients and reagents and culture conditions must be tightly defined and controlled. Batch to batch consistency must be underpinned by application of a pharmaceutical quality system and principles of Good Manufacturing Practice (GMP). The manufacturer must be licensed by an EU Competent Authority under the Medicines Directives. In the UK this is the Medicines and Healthcare Products Regulatory Agency (MHRA).

UK Blood Services have always been to the fore in the application of new developments in biotechnology from use of monoclonal antibodies to advances in transfusion and transplantation. We have also established a reputation over the years for delivering safe and effective therapeutic products derived from donated human tissues and cells. It is therefore not surprising that we are involved in this new area of cell based immunotherapy and regenerative medicine thanks to the generous support of our donors in giving us consent to use their donations for this research.

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Stem Cells and Immunotherapies

It is a great pleasure to witness the birth of the National Institute for Health Research NIHR-funded Blood and Transplant Research Unit (BTRU) in Stem Cells and Immunotherapies, hosted within the University College London UCL Cancer Institute. We are at a truly exciting time in the development of novel and effective gene and cell therapies, and the work of this unit will allow us to further develop and refine these therapies, and also to focus on developing the infrastructure to allow broader availability across the country. The unit will be a Centre of Excellence in human experimental medicine related to blood and transplantation with a strong focus on getting real benefits to patients. It aims to build on the expertise of UCL, the Institute of Child Health (ICH) and NHS Blood and Transplant (NHSBT) in these areas, facilitating innovative research and knowledge transfer, and enabling leverage of current infrastructure to build the capacity to support more widespread application of the exciting therapies that are emerging in the field. We have been fortunate to be able to bring together such an accomplished group of investigators with common purpose and hope to deliver transformative advances over the next five years. This includes colleagues at Queen Mary University of London under the umbrella of the UCL Partners organisation, longstanding friends and colleagues at King's College London, and industry partners at Miltenyi biotec.

As a brief background, all human blood cells begin as haematopoietic stem cells (HSC). HSC and their progeny, most notably the cells of the immune system, can be used to develop treatments for genetic disorders and cancers that affect the blood or indeed other organs. Haematopoietic stem cell transplants, the origins of which date back to the 1960s, remain one of the best examples of successful immunotherapies, wherein the donor immune system is harnessed to destroy cancer cells, generally leukaemia or lymphoma. However, the replacement of the patient's HSC with those of the donor also affords the opportunity to genetically modify the donor HSC to correct inherited genetic defects. Stem cell transplants carry significant risks, including relapse of the underlying cancer, infections or graft-versus-host disease, where immune cells in the donor blood attack the patient's body. The new BTRU will aim to address all of these areas, to develop novel immune and gene therapies, and to make transplants safer and more effective.

In order to do this we will be developing techniques to identify more appropriate stem cell donors, remove the immune cells that attack patients but not those that fight infection, and genetically modify immune cells to target cancer cells. The unit will also develop ways to use patient's own cells in treatments, avoiding the need for transplantation altogether and potentially offering new treatments for a wide range of human cancers. This work has the potential to impact on thousands of patients with either inherited genetic disorders or cancers and to rapidly transition new technologies and scientific knowledge into NHS Transplant services.

The work is structured into 4 overlapping Themes, each pioneered by a Theme Lead. Theme 1 is led by Professor Stephan Beck (UCL Cancer Institute) and focuses on improved donor selection or cellular composition of the graft to improve patient outcomes. Theme 2 is led by Professor Amit Nathwani (Royal Free Hospital) and focuses on gene modification of T cells in malignant disorders or inherited genetic disorders. This is a broad theme and has the potential to deliver a number of truly transformative proof-of-concept studies. Firstly, we aim to use gene editing tools to disrupt genes and make immune cells resistant to the effects of immune suppressive drugs so that they will function to fight infection even when patients are using heavily immune suppressive medications. Secondly, we will use gene editing technologies to repair defective genes, correcting an inherited defect in T cells which results in profound susceptibility to infections. Finally, Professor Nathwani and Dr Allison Blair will be investigating new targets for Chimeric Antigen Receptors (CAR) T cell therapies – these are therapies in which the patient's own cells are genetically modified to target and destroy their cancer, potentially avoiding the need for transplantation. I will be leading Theme 3, developing therapies that prevent or treat relapse following transplantation. This work will build on the pioneering work of Dr Martin Pule (UCL Cancer Institute), refining and improving further on current CAR T cell approaches.

The final Theme is led by Professor Adrian Thrasher (ICH) delivering perhaps the most far reaching vision of the BTRU in concert with Professor Waseem Qasim. I am delighted that both have committed to advance the automation of cell manufacturing, working in collaboration with Miltenyi biotec. These developments are critical to making these novel therapies more widely available to patients across the UK. They will work closely with NHSBT to transfer their knowledge to NHSBT facilities, leveraging the established infrastructure and manufacturing expertise of NHSBT to much broader application in this emerging field. This will be a major legacy of the BTRU, so a lot rests on their experienced shoulders! The clock is ticking.

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Core Skills & Knowledge in Transfusion

On behalf of NHS Blood and Transplant (NHSBT), the Organisation and Workforce Development Team provide education and training in all aspects of transfusion. The courses listed here are open to hospital staff.

Education and Training in Transfusion Science	
Blood Centre Tour	A basic overview of the NHSBT and Blood Centre laboratories.
Practical Introduction to Transfusion Science	A five day course to provide basic theoretical information and an introduction to routine practical techniques.
Specialist Transfusion Science Practice	A five day course to provide more complex and specialist level theoretical and practical information.
Advanced Transfusion Masterclass	A one day interactive study day comprising of talks and case studies, focussing in depth on one area of transfusion and/or transplantation.

Education and Training in Transfusion Medicine	
Non-Medical Authorisation of Blood Components	A four day programme for senior nurses and midwives who are working towards making the clinical decision and providing the written instruction for blood component transfusion.
Essential Transfusion Medicine and Intermediate Transfusion Medicine	To meet the training needs of Specialist Registrars and Clinical Scientists who are studying for RC Path part 1 exam. (free to SpRs training in England).
RC Path Revision Refresher Course	To Support specialist registrars studying for their RC Path part 2 exam.

Dates may be updated or cancelled.

For the latest information, please visit: http://hospital.blood.co.uk/training/ or email learning@nhsbt.nhs.uk

Develop your skills and knowledge in Transfusion!

Education and Training in Transfusion Science				
Blood Centre Tour				
Sheffield	**Filton (Bristol)**	**Manchester**	**Colindale**	**Newcastle**
23/02/16	21/04/16 17/05/16 16/06/16 26/07/16 18/08/16 20/10/16 24/11/16 20/12/16	06/09/16 12/01/17	16/12/15 26/07/16 07/09/16 30/11/16	19/01/16 10/05/16 18/10/16
Practical Introduction to Transfusion Science				
Sheffield	**Filton**	**Manchester**	**Tooting**	**Newcastle**
7-11/03/16 24-28/10/16	18-22/01/16 25-29/04/16 20-24/06/16 26-30/09/16	18-22/07/16 21-25/11/16 16-20/01/17	29/02-04/03/16 18-22/04/16 10-14/10/16	18-22/04/16 04-8/07/16 06-10/02/2017
Specialist Transfusion Science Practice				
	Filton		**Tooting**	**Newcastle**
	11-15/04/16 10-14/10/16		14-18/03/16 12-16/09/16	10-14/10/16
Advanced Transfusion Masterclass				
Sheffield	**Filton**	**Manchester**	**Tooting**	**Newcastle**
	23/02/16	06/10/16	22/03/16	23/11/2015
Essential Transfusion Medicine				
	Filton	**Manchester**	**Tooting**	
	27/06-01/07/16 05-09/09/16	10-14/10/16 30/01/-03/02/17	22-26/02/16 06-10/06/16	
Intermediate Transfusion Medicine				
	Filton	**Manchester**	**Tooting/Colindale**	
	04-22/07/16	08-26/02/16 06-24/02/17	13/06-01/07/16 07-25/11/16	

RCPath Pre Exam Revision				
	Filton 29/02-04/03/16 12-16/09/16 13-17/03/17	**Manchester** 14-18/03/16 05-09/09/16 06-10/03/17	**Tooting** 07-11/03/16 19-23/09/16	
Non-Medical Authorisation of Blood Components				
	Filton 14-17/03/16 19-22/09/16	**Manchester** 09-12/05/16	**Colindale** 03-06/10/16	**Tooting** 08-11/02/16

Dates may be updated or cancelled.

For the latest information, please visit: http://hospital.blood.co.uk/training/ or email learning@nhsbt.nhs.uk

CPD Questions

1. Blood Donation Mythbusters – Eligibility Criteria for Blood and Platelet Donors are decided by:

a) The Blood Safety and Quality Regulations.

b) European Directives.

c) World Health Organisation.

d) The Joint United (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee.

2. Donating blood after receiving a blood product or component since January 1st 1980:

a) Yes, if with blood derived coagulation factor concentrates.

b) Yes, if mother whose baby has required intra-uterine transfusion of red cells.

c) Yes, if with human specific immunoglobulin given as prophylaxis such as anti-D.

d) Yes, if with human normal immunoglobulin (IVIg).

3. Blood Donation after Travel:

a) West Nile Virus RNA test is required for donors visiting affected areas between 1st May and 30th November.

b) West Nile Virus is not a problem in the USA.

c) Donors returning from countries with endemic Dengue fever, always require a six month deferral.

d) Donors returning from countries with endemic Chikungunya Virus, always require a six month deferral.

4. Donor Selection Guidelines permanently excludes anyone who:

a) Has a tattoo.

b) Has used injectable self-tanning agents, such as Melanotan.

c) Has body piercing.

d) Has semi-permanent make-up.

5. Donation is kantian not utilitarian – Immanuel Kant was:

a) A Play-school Presenter.

b) A German Opera Singer.

c) A German Philosopher.

d) A 20th Century German Politician.

6. Correct Definition:

a) Kantian – individual in right to choose.

b) Kantian – societal justification.

c) Utilitarian – individuals right to choose.

d) Utilitarian – decided by Council Leaders.

7. Development of Eye Banking in the UK – The Cornea:

a) Consists of two layers.

b) Transmits less than 90% of light.

c) Is the major refractive component of the eye.

d) Is 5-7 cells thick.

8. Corneal Transparency critically depends upon:

a) Regular arrangement of collagen fibrils embedded in the Bowman's layer

b) Active control of stomal hydration by energy-dependant iron pumping mechanisms of the descemet membrane.

c) Regular arrangements of collagen fibrils embedded in corneal endothelium.

d) Active control of stromal hydration by energy-dependent pumping mechanisms of the corneal endothelium.

9. The first successful Corneal Transplant was reported in:

a) 1832.

b) 1961.

c) 1952.

d) 1906.

10. Non-medics are allowed to remove eyes from donors by:

a) Anatomy Act 1832.

b) Corneal Grafting Act 1952.

c) Human Tissue Act 1961.

d) Human Tissue Act (amended) 1986.

11. Over the last 10-15 years, changes in transplant techniques have resulted in:

a) Replacing full thickness of the cornea has increased.

b) Replacing full thickness of the cornea has decreased.

c) Replacing only those parts of the cornea that are dysfunctional.

d) Longer visual rehabilitation.

12. National Institute for Health Research Blood Transplant Research Unit in Organ Donation and Transplantation – The focus will be:

a) To increase the number of live organ donors.

b) Management of established transplant recipients.

c) Clinical pathway from identification of potential deceased organ donor to the implementation of the donor organ into most appropriate recipient.

d) Clinical Pathway from identification of potential live organ donor to the appropriate recipient.

13. The Four Key Objectives will <u>not</u> include:

a) Improve organ donor management and evaluate novel interventions in live donors.

b) Develop novel approaches for assessing deceased donor thoracic and abdominal organ quality.

c) Evaluate normothermic ex vivo perfusion.

d) Improved understanding of donor/recipient compatibility.

14. National Institute for Health Research Blood Transplant Research Stem Cells and Immunotherapy's – Will involve collaboration with NHSBT and, among others:

a) University College London.

b) Newcastle University.

c) Oxford University.

d) Cambridge University.

15. NIHR BTRU – Stem Cells and Immunotherapies: The overlapping themes does <u>not</u> include:

a) Improved donor selection or cellular composition of the graft to improve patient outcomes.

b) Gene modification of B cells in malignant or inherited genetic disorders.

c) Develop therapies that prevent or treat relapse.

d) Advance the automation of cell manufacturing.

Clinical Case Studies

Case 1

A 32-year-old lady, Blood Group (B R1r) received two units of red cell transfusion as her haemoglobin was 71g/l. Her post transfusion haemoglobin was 92g/l. Over the following five days, her haemoglobin dropped by approximately 1g/l each day. There was no evidence of bleeding.

Her Direct Antiglobulin Test (DAT) was 2 + C3d. Slight rise in reticulocyte count and a rise in a conjugated hyperbilirubinaemia, which the hospital thought to be a side effect of lenalidomide.

Her ABO blood group was B and the local transfusion laboratory picked up an antibody in the back grouping (that they could not identify). This was also recorded in pre-transfusion sample.

The Indirect Antiglobulin Test (IAT) was negative by LISS (Low Ionic Strength Solution) tube test 37°C and Column Agglutination Technology (CAT) negative by IAT at 37°C, but positive panreactive by enzyme. Therefore, sent the sample to the RCI Reference Laboratory for further investigations.

1. *What blood would you select and issue while awaiting further investigations from the reference laboratory?*
2. *What further information would you seek and clarify with the haematology Specialist Registrar before referring sample to reference laboratory?*
3. *What additional laboratory test would you investigate?*
4. *What is the value of using blood warmer if the antibody is detected at the following temperature?*
   a. *20°C saline agglutination positive, negative at 30°C.*
   b. *20°C and 30°C positive and negative at 37°C.*
   c. *30°C and 37°C positive.*
5. *What is the likely diagnosis?*

Case 2

1. A G2P1 36-yr-old patient, Indonesian female, was seen at the antenatal booking clinic. She was investigated following the birth of her first child due to a blood group discrepancy and was documented as Ah Para Bombay.

   What do you understand by Para Bombay blood group?
2. Reference laboratory confirmed Ah Para Bombay with the presence of weak anti-H.

   What advice would you give to Obstetrician looking after the patient for antenatal care and transfusion support?
3. *For elective procedure what blood would you provide?*
4. *For urgent transfusion support what blood would you select?*
5. *When issuing incompatible units in a recipient with underlying clinically significant antibodies in urgent situation (with no time to locate antigen negative units; or no time to order suitable antigen neg unit from national frozen blood bank) what options or consideration should be taken?*
6. *What are the potential side effects of Intravenous Immunoglobulin (IVIG)?*

Answers to Clinical Cases

Case 1

1. Clinically significant antibody not detected at 37 by IAT. Select B Rh K matched cross matched by LISS tube IAT or CAT 37°C IAT.
2. As there was no clinically significant RBC antibodies by IAT at 37°C and patient is haemolysing it is important to review the blood film, morphology and FBC indices. Review showed red cell agglutination on slides and FBC indices were suggestive of CHAD.
3. It is important to establish the thermal amplitude and test should include LISS direct saline agglutination at 20°C, 30°C and 37°C[1].
   a. Reverse ABO grouping positive both with anti-A and anti-B (picking up cold antibody reacting at RT).
   b. DAT by C3d only.
   c. Need to confirm thermal amplitude for diagnosis of Cold Haem Agglutinin Disease) CHAD.

   In general titration studies and specificy test are not essential for diagnosis of CHAD, might be indicated in selected cases. CHAD is defined as cold antibody reacting (by direct agglutination test) at or above 30C°.[2]

4 Using blood warmer is a subject of debate <u>but will not cause harm</u> (in situation 3b and 3c) especially if thermal amplitude is 30°C as warming blood to 37°C will have some protected action.

5 CHAD with cold antibody reacting at 30°C/there is only one case report of CHAD associated with Lenalidomide.

References:

1. Immune Haemolytic Anemia 2nd ed LD Petz and G Garraty Churchill Livingston. Pg 186.
2. Plasma exchange and rituximab treatment for lenalidomide-associated CHAD Transfusion: 2012; **52**:2432-2435 Brauer *et al.*

Case 2

1. **Para Bombay phenotype.** Total absence of H antigen on RBC and in secretions together with a potent anti-H defines the Bombay (Oh) phenotype and is extremely rare. Also uncommon is the **Para Bombay (Ah or Bh) phenotype.** These individuals have a very low level of ABH antigens (depending on the ABO genotype)Para Bombay individuals retain some H antigens on RBCs either as a result of a weakly active 2-FucT or from uptake of soluble H from plasma.
2. Little information exists on the clinical significance of anti-H in Para Bombay.
3. For elective procedure and if time permits and if available – provide bombay or Para Bombay unit.[1]
4. For urgent transfusion support select least incompatible ABO matched (K matched) units. Still it is worth check/ discuss with NHSBT Consultants regarding availability of the rare units.
5. When issuing least incompatible units IVIG / steroids have been tried either before or within 24 hrs of transfusion to suppress or ameliorate the reaction. IVIG is not recommended for either the prophylaxis or routine treatment of haemolytic transfusion reactions. Based on consensus by the expert panel, IVIG may be considered as an option among supportive therapies for urgent situations in this disorder[2].
6. Although IVIG is generally considered as a safe product, adverse reactions ranging from mild, self-limited to severe have been reported. Infusion of IVIG has been associated with renal toxicity, thromboembolic events and haemolytic reactions (rare events of significant haemolysis have been reported more commonly in blood group A recipient[3]).

References:

1. The clinical significance of blood group antibodies.. Daniels G, Poole J, de Silva M, Callaghan T, *et al. Trans Med.* 2002; **12**: 287-295.
2. Guidelines on use of IVIG for Hematologic Conditions. Anderson, D. *et al.,* 2007. *Transfusion Medicine Review **21** (2) Suppl 1, ppS9-S56) from the IVIG Haematology and Neurology Expert Panels, Canada.*
3. Acute haemolysis after high dose IVIG therapy in highly HLA sensitized patients. Kahwaji *et al. Clinical Journal of the American Society of Nephrology 2009 **12**; 1993-1997.*
4. Management and transfusion support for a pregnant woman with Para Bombay phenotype. Lee *et al. Vox Sang vol **109** Suppl 1 June 2015.*

Diary Dates

2016

27 February
FRC Path 1 Revision Course
Location: Kingston Hospital, London
For more information contact:
www.b-s-h.org.uk

12-14 March
The London Haematolpathology Course: A practical integrated approach to the diagnostic haematological malignancies
Location: Barts and The London School of Medicine and Dentistry, The Royal London Hospital, London
For more information contact:
www.b-s-h.org.uk

25-27 March
FRC Path 2 Mock Revision Course
Location: Education Centre, Kingston Hospital, London
For more information contact:
www.b-s-h.org.uk

12-15 April
British Group Serology
Location: Bradford College, Reading
For more information contact:
www.bbts.org.uk

18-21 April
BSH Annual Scientific Meeting
Location:
For more information contact:
www.b-s-h.org.uk

11-14 May
20th Training Course on Haemopoietic Stem Cell Transplantation
Location: Budapest, Hungary
For more information contact:
www.esh.org/conferences

21-22 May
Biennial Meeting of the European Society of Paediatric Haematology – Immunology
Location: Langenbeck-Virchow-Haus GbR Luisenstraße 58/59 10117 Berlin (Mitte)
For more information contact:
www.b-s-h.org.uk

27 June
Deconstructing Donation Study Group Conference
Location: Lancaster University, Lancaster
For more information contact:
www.britsoc.co.uk/groups/deconstructing-donation.aspx

18-19 July
An Introduction to Immunology
Location: University of Warwick, Coventry
For more information contact:
www.b-s-h.org.uk

6 September
Moving Forward with Stem Cell Therapy
Location: Cineworld: The 'O2', Peninsular Square, London
For more information contact
www.b-s-h.org.uk

Notes

CPD Blood and Transplant Matters

Answers Issue 46

1. D (But also A and C – dangers of acronymys)
2. D
3. B
4. C
5. A
6. B
7. A
8. C
9. B
10. B

Notes

Notes

Blood and Transplant Matters is prepared
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