



BONE MARROW TRANSPLANTS FOR PRIMARY IMMUNODEFICIENCIES

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Dedicated to the Memory of Nicholas Jowett and Tanya Chaudhery

FOREWORD *by Fiona Sandford*

Since 1968, bone marrow transplants (BMTs) have been an important treatment for primary immunodeficiencies. Until relatively recently, BMTs were limited to babies with Severe Combined Immunodeficiency (SCID). More recently, as the nature of different immunodeficiencies has become better understood, and as techniques in bone marrow transplants have improved and so lessened the risks, families with conditions such as Wiskott-Aldrich, Hyper IgM and other combined immunodeficiencies are being offered the choice of a bone marrow transplant.

This booklet is designed to help families facing BMTs. I wrote about my family's experience of our son Kit's transplant for the PiA's newsletter *Insight*. The response to that article was overwhelming and clearly indicated that there was a lack of written information on the subject. In this booklet, Dr Andrew Cant gives the medical background to bone marrow transplants and immunodeficiencies, Judith Armstrong, the BMT nurse co-ordinator at Great Ormond Street Hospital, gives some practical advice on preparing for transplant, and Rebekah Lwin, Clinical Psychologist also at Great Ormond Street Hospital, discusses the aftermath and recovery period. In addition, five families who have recently lived through BMTs tell of their experiences. These families have children of different ages, with different conditions and different types of transplant. They have written candidly about this most difficult period, and the PiA is very grateful to them for having the courage to share their experiences. One of the side effects of the drugs used in transplant that greatly concerns families is the possible effects on future fertility. Recent developments have allowed some families to take steps to try to minimise this risk, and this is discussed in the article by Dr Alison Leiper and Rebekah Lwin.

Each bone marrow transplant is different. BMT centres have different physical facilities, and therefore different practices. Children react differently to the drugs used, and experience different side effects. For some families the period before transplant is the hardest, for some the time in hospital is most difficult and for some the recovery period causes the most problems.

BONE MARROW TRANSPLANTATION FOR PRIMARY IMMUNODEFICIENCY

by Dr Andrew Cant, a member of PiA's Medical Advisory Panel, senior lecturer in child health, consultant paediatric immunologist and director of the Primary Immunodeficiency Unit at Newcastle General Hospital

Why consider bone marrow transplantation (BMT)?

To answer this question we need to remember the immune system's origins. White blood cells are the key players in our body's immune system and arise from a population of self-perpetuating bone marrow cells called stem cells. As these divide and multiply some of the daughter cells become new stem cells whilst the others develop into different blood cells - red cells, platelets, neutrophils, monocytes or lymphocytes. The most severe forms of Primary Immunodeficiency, particularly those seen in childhood, are due to genetic faults which prevent the proper development or function of one of these groups of cells, and exciting research in the last few years has pinpointed these defects. In X-linked agammaglobulinaemia (Bruton's Disease) a fault in the gene, or blueprint for a messenger molecule called Bruton's Tyrosine kinase, prevents B-lymphocytes developing from progenitor cells in the bone marrow, so patients cannot make antibodies. Patients with the B-positive Severe Combined Immunodeficiency (SCID) cannot make a special molecule on the surface of lymphocytes and so cannot receive the signals necessary for growth and development of those cells. Such children lack T-lymphocytes and have B-lymphocytes that cannot produce antibodies. The loss of these two major parts of the immune system means that even trivial infections are fatal. The best treatments for primary immunodeficiency are those which fully correct the particular deficiency. When B-cells fail to develop, infusions of antibody in the form of intravenous immunoglobulins (IVIg) completely correct the problem.

In SCID, however, although IVIg will replace antibodies the B-lymphocytes cannot make, it cannot restore T-lymphocyte function and children still die of infections with viruses which only T-cells can eliminate. The only way to treat severe T-cell defects is to replace the faulty self-perpetuating stem cells with ones without the genetic faults and so allow the development of normal T-cells. Because stem cells are self-perpetuating, as long as this new bone marrow remains viable, the patient is cured. SCID was first successfully treated by bone marrow transplantation in 1968, using the patient's brother as a donor. The patient is still alive and well, and her brother's bone marrow stem cells are still dividing, replicating and giving rise to a fully functioning immune system.

How does BMT work?

Bone marrow cells carry distinct identification tags on their surface, known as tissue types. We inherit half our tissue types from one parent and half from the other. Tissue types are extremely important as they enable us to recognise and destroy foreign cells. Without them we could not deal with invading bacteria and viruses, as happens in Bare Lymphocyte syndrome, where tissue types are not made.

However, if bone marrow from a person from one set of tissue types is given to a person with a different set, the two systems recognise each other as foreign and fight! If the recipient's immune system gains the upper hand the donor's bone marrow is rejected; if the donor's system wins, then the patient develops a severe inflammation in the skin, liver and gut, known as Graft-vs-Host Disease (GvHD) which can be fatal. Because brothers and sisters each inherit tissue types from the same parents, there is a one-in-four chance that a brother and/or sister will have inherited the same tissue types. When using bone marrow from such a brother/sister, the risks of graft rejection or GvHD are low and such transplants are the most successful.

Although unrelated people carry different tissue types, the number of types is not endless, and by chance, two out of 18,000 people will share more or less the same tissue types. Because of good will, it has been possible to set up registries of several hundred thousand people across the world who are willing to donate bone marrow. In this way patients can be matched with unrelated donors whose tissue types are almost as exactly matched as brothers and sisters who share the same tissue types.

In the last fifteen years it has also proved possible to use bone marrow of different tissue types - so called mismatched transplants. This has really only been successful in SCID and even then it is a difficult technique, as the T-lymphocytes (which are mainly responsible for GvHD) must be removed from the donor's bone marrow before the marrow is infused into the patient. Although this largely prevents GvHD, it increases the chances that the marrow will be rejected, and also greatly increases the delay before the new immune system functions, so increasing the risk of infection. Nevertheless, with meticulous painstaking care, such BMTs are often successful, particularly for infants with SCID who cannot easily reject marrow.

What are the pros & cons of BMT?

Having identified a suitable donor, the patient must be carefully assessed. It is important to detect infections that may have already damaged the lungs or liver, as problems here reduce the chances of a successful transplant. The patient is then admitted to a sterile environment and their own marrow destroyed with powerful drugs, usually used for treating cancer, or sometimes a mixture of these drugs and radiotherapy. By wiping out the patient's immune system the risk of rejection is largely prevented, but infection becomes a risk. After ten days of this treatment, marrow is taken from the donor under a general anaesthetic by pushing a needle into the donor's pelvic bones and collecting some marrow. The donor may feel a little uncomfortable for a few days, but quickly makes up for the marrow that has been taken, and providing the donor is in good health, this procedure carries only a tiny risk. Marrow is infused into the patient like blood into a vein and we then wait whilst the donor marrow cells find their way to the patient's bone marrow cavity, start multiplying and after two to three weeks, begin to appear in the blood. During this time the patient produces no blood cells and needs infusions of the platelets. A very careful watch is kept for signs of infection which is treated very promptly and thoroughly. Sometimes there is a degree of GvHD when the new marrow cells start to appear, or 'take'. This may require treatment with immunosuppressant drugs. Occasionally the marrow is rejected and the patient's own marrow reappears, and both rejection and GvHD increase the risk of infection. About six weeks after the graft takes, the patient's new immune system starts to develop, and a little later they can go home, although antibiotics and IVIg are often needed for up to a year whilst the new immune system fully matures. Successful bone marrow transplantation is usually curative and it is very exciting to see poorly, sick patients transformed into normal healthy children. However, when unsuccessful, usually because of rejection or Graft-vs-Host Disease, patients often die from infection. A few patients remain unwell after a BMT because the graft has only partially taken, or because of ongoing GvHD, but by and large BMT is either fully successful or not successful at all. When a baby has SCID, which untreated is always fatal within a few weeks or months, decision-making is not difficult and doctors and parents wish a BMT to be attempted, unless the child is so severely ill with infection that the chances of success are negligible. In other immunodeficiencies where patients can remain relatively well for a number of years if given IVIg and antibiotics, decision-making can be more difficult.

Which patients and why?

Bone marrow transplantation is the only way to give new T-cells or phagocytes and so T-cells and phagocyte immunodeficiencies are the main indication for BMT. When T-cells do not work at all (as in SCID) BMT is essential. In other T-cell immunodeficiencies with partial T-cell function, matters must be considered more carefully. At present Wiskott-Aldrich syndrome and the Hyper IgM syndrome (CD40 Ligand deficiency) as well as some types of combined immunodeficiency (many of which we now know to be minor forms of SCID) are the main indications for BMT. If there is a brother or sister who shares the same tissue types, or an unrelated donor who is well matched, then many of these patients will benefit from BMT. Patients with Chronic Granulomatous Disorder (CGD) and a tissue type identical brother or sister, are also now being considered.

When asking the question: "Is bone marrow transplantation the right treatment for patients with immunodeficiency?" it is helpful to ask the following questions: -

- Does the patient have a T-lymphocyte or phagocyte deficiency?
- Is the patient already receiving the best possible other forms of treatment? (For example, IVIg and preventative antibiotics)

- What is the likely future course of the patient's condition? What will their future health be like? How disabled will they be and what life expectancy do they have?
- Is there a suitable donor? (If there is a tissue type identical brother or sister, or a well-matched unrelated donor, BMT will be less risky.)
- Has there already been serious infective damage to the patient's lungs or liver which would make transplantation more risky?
- What do the patient, parents, doctors and nurses together feel is the best course of action?

Our understanding of primary immunodeficiency diseases and our expertise in bone marrow transplantation are rapidly improving, so the answers to these questions are changing! Careful follow-up of patients and pooling of data between treatment centres - a successful example of European collaboration - has taught us a great deal about the longer term outlook for T-cell immunodeficiencies such as Hyper IgM syndrome (CD40 Ligand deficiency) and Wiskott-Aldrich syndrome. We now know that the long-term risks of liver disease in Hyper IgM and cancer of the white blood cells in Wiskott-Aldrich syndrome seem greater than was thought. At the same time, BMT from a matched brother /sister or unrelated donor is proving successful in over 80% of cases, and younger patients without serious liver or lung damage do best. In CGD there is concern that although patients can remain healthy in childhood, serious problems may arise in early adult life, so BMT is being advocated if there is a matched brother/sister donor.

The government funds a national programme for the assessment and treatment of children with severe forms of primary immunodeficiency, centred around units in London and Newcastle. Once referred, each patient is carefully assessed in the light of the most recent scientific information and matters are fully discussed with all concerned. In this way the best treatment is worked out on an individual basis, balancing the risks and benefits of BMT against the risks and benefits of continuing with the best possible supportive care. The more severe the immunodeficiency, the younger the patient, the less severe the damage to lungs and liver from any infection, and the better the match of any potential donor, then the more there is in favour of carrying out BMT.

Advice is changing and we realise that this can be unsettling for families who had previously not considered BMT, or had been told that BMT was not the best treatment for their child. We also very much recognise the dilemma of considering a BMT for a child who is currently very well, but who may become unwell in three, five, ten or fifteen year's time. This dilemma is made all the more difficult because BMT is most likely to be successful in such a well child, whereas if one waits until serious infection has set in, this makes BMT a much more risky undertaking. Although decision-making can be hard, successful results are so encouraging and it is remarkable how much better children can be when they have been given a new immune system. •

PATRICK'S STORY ...SO FAR!

Patrick was born with Wiskott-Aldrich Syndrome. His story is written by his mum Susan

Patrick first had problems aged six weeks with an unusual infection on his cheek which did not respond to oral antibiotics. More infections followed, always requiring treatment with intravenous antibiotics. A blood sample showed he had insufficient platelets' although they were thought to be normal size. This was diagnosed as ITP (idiopathic thrombocytopenia) Many of these infections were in his upper airway and a bronchoscopy at four months showed he had a throat problem (diagnosed as laryngo malasia) which was thought to be the reason for the piercing cough he had - he regularly sounded like a Jack Russell.

We continued with this diagnosis until Patrick was 20 months, with him having recurring infections, on average involving a hospital admission once a month for intravenous antibiotics. His platelet count was checked on a weekly and then monthly basis and it ran at levels between 20 and 45. Then one night, when we were in our local hospital for yet another throat infection, Patrick's oxygen levels began to deteriorate and within a matter of hours he was in intensive care on oxygen and still failing to pick up. His throat had nearly closed up with the severity of the infection, and he was transferred 55 miles by ambulance to Sheffield Children's Hospital where an emergency tracheotomy was performed and we were taken aside to be told that he also had, in all probability a Primary Immunodeficiency called Wiskott-Aldrich Syndrome. We were told that it was a very serious condition and that he would continue to suffer from recurrent and probably increasingly serious infections, any one of which could prove fatal.

After the initial shock, my husband and I decided we had to concentrate on the fact that we had a child in intensive care and we had to learn to look after a child with a tracheotomy and we just couldn't deal with Wiskott-Aldrich at that time. We deferred the task of understanding this complicated syndrome until we had more time. There was also a feeling of regret and indeed anger that it had taken Sheffield Children's Hospital a few hours to diagnose a child who had been poorly for most of his life - why had we not known before? A Bone Marrow Transplant was discussed at this time but as his brother was not a match, it was discounted.

A few weeks later we came home. Patrick had in the meantime been started on prophylactic Septrin and the infections to all intents and purposes stopped. Most of the problems over the next few years were connected to his tracheotomy (he fell head first in slime filled fish pond), and he continued in good health after the tracheotomy was taken out when he was three and a half.

Life pre-BMT

We were seen every month or so by a consultant paediatric immunologist (Dr Adam Finn) at Sheffield Our local paediatric consultant also kept in touch, as did our GP. Life was now almost normal - although infection remained a worry, Patrick was a healthy child and only had one unplanned hospital admission in the next two years when he caught chicken pox and was admitted, as a precaution, for intravenous Acyclovir. His other problems were bruising - he always had a large bruise on one temple or the other - and increasingly eczema. These did not stop us having a normal family life. He went to playgroup, school, on holiday at home and abroad, had swimming lessons and as long as we had Septrin and a tube of unguentum merck we were fine.

The BMT option

In late 1996, Dr Finn referred us to Dr Andrew Cant in Newcastle General Hospital to have a chat about developments in the prognosis for Wiskott-Aldrich (poor because of cancers of the immune cells, lymphoma) and the success of Bone Marrow Transplants (improving but still only 60-80% for matched unrelated donor transplants) Our first appointment was on 19th December 1996. They concluded that Patrick was a prime

candidate - he was just about young enough (five), he was healthy and with a well matched, good quality donor he stood a good chance of making a full recovery.

We agreed that they should look for a donor - in our minds saying nothing is decided yet, maybe they won't find one and we won't have to make a decision. We knew however, that we had consented to the start of a process that had descended like a huge black cloud on our family. We didn't seem to need to talk about it very much at this stage and after a few months had slipped by with three potential donors having been discounted, we forced the whole thing to the back of our heads and had a great holiday in New England. Three weeks after getting back, Dr Cant telephoned to tell us that he had good news - a well matched, high quality donor had been found from the Anthony Nolan Register and they would like Patrick to be admitted in three to four weeks, if we wished to proceed.

The decision

The decision had been made by the time we came to make it- if that doesn't sound too foolish. However far back we had pushed it over the previous nine months it was there all the time - an ever present sadness of what we would have to face, what Patrick would have to face if it went ahead or not. We felt there was very little anyone else could say or do to help us decide - clinically it was a relatively straight forward decision, this was the recommended course of action by the leading experts in this country, in America and in Europe. Emotionally there was no right answer. How could we agree to let our well (on the outside) child go through this life threatening treatment on a 70/30 chance that it would work? How could we live with ourselves if it didn't - if he died? What would we then say to his brother? I cried a great deal during this time - the pain of the decision became a physical as well as a mental one. There was no place to go for comfort. We both knew we were going to say yes because in the end we couldn't justify saying no - if this was his best chance of leading a normal life then we had to give it to him- but it was the most difficult decision we had ever had to make. It was the blacker of the possible outcomes I rehearsed in my head - what would I say at his funeral? Would we be able to continue to live in the same home, town, be with the same friends if it all went wrong? It went round and round with no satisfactory solution - none that brought any peace of mind.

Life on the BMT unit

We arrived at Newcastle on 3rd November 1997. First Patrick had his Hickman line put in under a general anaesthetic and we then waited for a couple of days at the 'halfway house' - a house that belongs to the unit at NGH used by families on their way in or out of the unit. Patrick went 'under the flow' on 7th November and chemotherapy started the next morning. We learned how to scrub up - a two-to-three minute hand-and-arm wash which you had to do every time you went into your child.

In many ways things were better once we were in NGH. All the organisation was over - my husband arranging time off work, my sister fortunately being available to look after our other child, telling those who needed to know what was happening, (I found this very emotional as people were not surprisingly very sympathetic and sometimes it was overwhelming), and deciding what to bring. Patrick walked across 'the line' without a backward glance and never stepped out until he was allowed to. The first night we were told we were not allowed to kiss him good night - another low. In NGH you are not allowed to sleep with your child - this was a real problem whilst he got to know the staff. The chemotherapy took its toll after five days and Patrick became very sick- vomiting, diarrhoea, ashen and very unhappy. This improved as his bone marrow was destroyed and by the day of the transplant he was a little happier. The marrow safely arrived, always a worry, and was infused through his line - a pink milkshake in a bag - it took about an hour. Then began the waiting period - anxious days of blood results when nothing was happening. By this time Patrick was so nauseous that he had stopped eating and was on full IVTPN (total parental nutrition). He was still being sick and having diarrhoea but we played draughts, chess, dominoes and snakes and ladders, and we watched videos including Toy Story 11 times in the first three weeks (and a great movie it is!). By Day +21 nothing had happened so they decided to use a catalyst called GCSF, to stimulate the marrow. This worked and the counts of white cells and later, neutrophils, very slowly began to climb.

Each day on the unit went much quicker than we had thought - there were always people coming and going. These included a daily visit from a doctor, many nurse visits - social and for the administration of many IV drugs and frequent checking of temperature, blood pressure, weight and general well being, and occasional visits from the pharmacist, teacher, dietician, physiotherapist, social worker, family support worker and chaplain. The atmosphere was on the whole good. We developed a good working relationship with the staff, each person playing their part in the process. The staff were always there when we needed them and although there were many worrying moments we were fortunate that Patrick never became so ill that we lost hope. All the problems which he encountered had previously been mentioned to us as possibilities and so were less frightening as a consequence. He suffered from haemorrhagic cystitis, papova virus, pneumonitis, mild graft versus host disease, high blood pressure, a magnesium deficiency, E.coli urinary infection, adeno virus and a line infection.

Patrick was sometimes rude and aggressive to the doctors and nursing staff much to our embarrassment. We did try to encourage continued good behaviour but this was a constant struggle. My husband and I had decided to share the load between us but Patrick decided that he wanted his Mum and again this was difficult - my husband had to endure some very harsh words to give me time out. I then found I couldn't relax knowing my son was feeling the way he did and yet I couldn't be there all the time. I spent two nights away from Newcastle in three and a half months, on both occasions to do something for my other son - Patrick did not make leaving a painless experience.

By Christmas it was decided that Patrick should come off TPN to encourage him to eat - this is often a major problem we were told, and certainly it took over two months from then before eating was back to near normal. Patrick ate a Curly Wurly for Christmas lunch and we all cheered. Diet is restricted for some time - food and liquid has to be sterile, (so mostly tinned or frozen), and prepared by parents in the microwave. Newcastle United FC came to visit which was exciting for us all - Stuart Pearce gave Patrick a fluffy rabbit and my husband, a Celtic supporter, met his schoolboy hero, Kenny Dalglish. Patrick was six at the end of January and so we made Rice Krispies and buns in the microwave and had a little party - we played pass the parcel in and out of the flow, we all sang and Patrick blew out his candles.

By now his neutrophil count had risen to over one and he was allowed to go out to a small courtyard with either a parent or a nurse to play. At the beginning his legs were very weak but gradually, and with some physio input, he became stronger. Patrick also became a play station addict playing FIFA 97 and 98 at any opportunity and he collected Premier League stickers- he studied the sticker book from cover to cover very happily. He also did some schoolwork most days although the amount depended on how well he was feeling, but we feel he has not fallen behind over the months away.

Coming Home

We came home on Valentine's day. We arrived at our house to find balloons, banners and a yellow ribbon to welcome us. The boys (we can still say that) ran off to look at the decorations and for us the strength of feeling that welled up brought us both to tears. We had never let ourselves believe that this day would come and here it was - we were all home.

We had a great week - it was half term and the weather was warm. We spent our time in the garden and Patrick was happy and eating well. He continued to be sick from time to time but this became less and within six months post transplant appeared to have stopped. At first the change of scene did us all good. After perhaps a month the restrictions of this next phase started to cause their own problems. We could go to the park, for walks in the countryside and to the shops when it was quiet. The problem was that it kept raining and we couldn't go indoors to museums, theme parks, swimming pools, cinemas and bowling alleys nor could we eat out. Picnics in the car in the rain just aren't the same. Our local education authority provide two hours home tuition a week so I have taught Patrick at home. This has worked well on the whole but again as the weeks wore on it has been more difficult to maintain his interest.

For the first three months or so we had to vacuum and damp dust all the areas Patrick used, every day - quite a big job in our Victorian house with 'dust-trap' skirting boards. His bed-clothes and pyjamas had to be changed every day and all had to be washed at 60 degrees and dried in the dryer. At first Patrick and his brother were allowed one designated friend each and this has now been increased to two. Healthy adult friends may visit although we found we didn't rush to have too many people round as Patrick didn't seem to want to have too much to do with them and we were concerned about the risk of infection.

So at eight months post transplant, and five months out of hospital, life is still fairly restricted and we still say, "So far so good," and, to be honest, we are all pretty fed up. We so much want a normal life back and yet we know there is still a significant way to go. Patrick's counts, (of T cells and B cells), are continuing upwards slowly. He remains on a variety of medication (approximately 24 tablets per day) and a three weekly infusion of immunoglobulin. He has a thumb prick blood test twice a week at our local hospital to check the level of Cyclosporin in his blood. We visit Newcastle General Hospital every six weeks.

Final thoughts

I do not feel in a position to offer advice as such - the hard bit, the decision, is such a personal one. It may help to know that the dilemma is similar to the one others have faced and they, like you, did the best for their child in their situation.

I also feel that people should prepare themselves (and their friends and family), for a long haul. It is a life changing experience which will tax your emotions and your energies. We hope to regain our zest for life but just now most things seem unimportant compared to the task in hand. I think we were not prepared for the length of time it would take to get back to normal, and at the time of the BMT it didn't matter as we hardly dared hope we would reach that stage - but it matters now, and I feel my family would be less frustrated by the limitations if we had known more of what they might be.

You might find it useful to know? that we had intended to install a new bathroom and to carry out various decorating projects - we have not been able to proceed with these as the bare plaster which would be exposed would carry a health risk for a recently transplanted child

Have we made the right decision? The jury is still out on that one - but we hope so. •

CHARLIE'S STORY

Charlie was born with Severe Combined Immune Deficiency. This is his story, written by his mum, Jane

Charlie White was born on 27th March, 1997, by emergency Caesarean, because he was an undiagnosed breech baby and large at nearly 91bs. He was a beautiful, perfect baby boy I was in hospital for seven days after his birth and during this time he was difficult to breast-feed: I had to have a nurse help me with each feed. I thought something was wrong because I had breast-fed my three older children with no problems. I was told that babies born by Caesarean do not suck as well, and to give it time. When we went home I was still finding it difficult to feed him.

After two weeks he was under his birth weight and covered in a rash. I was admitted to hospital with him, but the doctor could find no reason for the rash and could find nothing else wrong. After much thought he was put on SMA for day feeds and breast-fed during the night. After a few days I was sent home and things went well for a while. I was feeding on demand which was almost constant. Charlie then developed a choking cough. I took him to my GP who said it was a virus and it would pass. The cough got worse and I went back several times, taking my daughters and Charlie's father to describe the cough because I thought I was not explaining it properly I saw all the GPs at the practice

but they could find nothing wrong with him and I was told it was a virus and that he would grow out of it.

It came time for his injections; I checked beforehand whether he should still have them and was told it was OK to go ahead. Charlie's cough got worse so I took him to a homeopathic doctor. He suggested changing Charlie's milk to soya. (By this time Charlie was not breast-feeding at all, even though I had plenty of milk). The homeopathic doctor gave me several remedies but with little results. Charlie's cough bouts were now several times during the day and night and by this time I was desperate, having little sleep. One day when we were out Charlie started coughing. I was in the car with him; he went blue and I could not hear him breathe. We rushed to the nearest hospital accident and emergency department. He was given oxygen and he began to look better. They said that they would like to do more tests so I was admitted with him to hospital. He was given a lumbar puncture for meningitis, but it was clear. They also tested him for whooping cough and that was clear too. He had now started to vomit after his feeds. We were in hospital for over a week, but they could find nothing wrong although he was clearly unwell. We were told it was a virus and it would pass. I was desperate to go home. I was very unhappy in hospital, but I was also unhappy about taking him home, because he was clearly not well. One of the nurses said I should stay until they got to the bottom of what was wrong.

But home we went with Charlie coughing and vomiting. I was desperate and no one would listen to me. I did not think it was a virus. My health visitor came one morning when I was at breaking point, and she arranged with the local hospital to get me a monitor for Charlie's cot so perhaps I could sleep. An appointment was made to see the Resuscitator Officer. When he saw Charlie he just looked at him, and when I told him my story he said I needed a second opinion. He said he would do what he could, but that I needed to be referred by my GP whom I rang again. When my GP saw Charlie he referred us back to the Conquest Hospital and we were admitted. Charlie was now on constant oxygen and vomiting much more. He was given a test for cystic fibrosis which was negative. I felt that we saw every doctor at the hospital and none of them could find what was wrong. We were then referred to Great Ormond Street Hospital and admitted. They repeated all the tests he had already had plus a test which showed mild reflux and a hiatus hernia. In the end Charlie had a lung biopsy and afterwards he was in intensive care. He was diagnosed as having Interstitial Pneumonitis (an unusual pneumonia) and he had also contracted MRSA (this cleared up on its own). He was put on a high dose of steroids and drugs for reflux. We were told he could be on oxygen indefinitely. We were then referred to the immunology team who came to see us. I was asked to take an AIDS test. I was quite shocked but I knew it could not be that. My test and Charlie's were negative. They were also worried about his kidneys at this time. Charlie slowly picked up and after a month we were transferred to our local hospital, and there he came off oxygen. Then we went home. After two weeks we had an appointment with the immunology team at Great Ormond Street. We were told he had an immune problem and they would like to do more tests. They thought that he might need a Bone Marrow Transplant or that they might be able to manage him on immunoglobulin and antibiotics. I had to keep him away from unwell people and keep in contact with GOS. We were to be referred to Dr Davis and Dr Jones.

On the way home from Great Ormond Street, Charlie started to scream in pain and he had very bad diarrhoea. He screamed all that night, and first thing in the morning we took him to the Conquest Hospital - green bile was removed from his tummy but he could not stop crying in pain. We were referred back to GOS and admitted again. The doctor was called out late at night but he could find no need for an operation, so Charlie was treated with antibiotics. By this time his diarrhoea was constant and he got very dehydrated. Charlie then had his first Hickman line fitted. He kept getting well, then sick again and he also had several line infections. He was also given a gut biopsy. The results showed severe damage and we were told that Charlie's only hope would be a Bone Marrow Transplant. The search was on for a donor. Charlie had Severe Combined Immune Deficiency A match in this country could not be found so they looked abroad. Meanwhile Charlie kept getting infections, in his tummy, in his Hickman line and once they suspected he had meningitis. Another lumbar puncture was done. He was on his way to intensive care but suddenly he began to pick up. By this time he had had four

Hickman lines. It was like living on a knife edge waiting for news. Each time he got sick we wondered would he recover this time? The staff on Giraffe ward worked so hard for him - their care saved him.

Eventually news came they had found a bone marrow match in this country. A good match too 9.5 out of 10. Everyone was so pleased, I shall never forget that morning the look on everyone's faces. We met the consultant on Robin Ward - he laid everything on the line. Without a transplant, Charlie might not live beyond two years but because of his lung problems, a severely damaged gut and an enlarged liver, they were not sure how he would cope with the chemotherapy. Also they feared that after transplant he might continue to have feeding problems he could possibly be on long term TPN (intravenous feeding) or he may need to be tube fed. We could be in hospital some time.

We moved to Robin Ward at the end of March and Charlie was the best he had been for months. Transplant was set for 1st April. Charlie seemed to know something was going on. We started the chemotherapy He took this orally - he was always good with all his medicines. The side effects started straight away, he was very sick and had even more Diarrhoea. The staff kept the diarrhoea and sickness under control as best they could. The transplant day came and went without any problems for Charlie although my daughter had to go home from work because she was so worried.

Now the waiting began: would he reject the new marrow? We were told he would now get very sick- but he did very well, and each day he got better and happier. The doctors and nurses and childminders were wonderful working so hard for Charlie and for me. It was a very difficult time but nothing was too much trouble for them. Gradually his counts came up and the Green Sticker (which signals the most stringent precautions) came off the door. Charlie could go onto the ward and play with the other transplant children. He was so happy, and he was soon well enough to come home. Plans were made to spring clean the house and car and remove our much loved pets.

We came home, but Charlie became unwell and was vomiting his very important medicines so I had to return to GOS for another week. After that he was well enough to return home. My house has never been so clean with constant washing, my children only have close friends to the house and so do I, and all visitors are checked to make sure they are well. We have been home for four months now, just waiting for Charlie's immune system to work on its own when we can catch up and lead a normal life. Charlie's T cell function is slowly improving he is feeding well and just starting on solid food.

Everyone has worked and cared so much for Charlie and for our family. Without their kindness and help I don't think things would have worked out as they have done. I can't really find the words to describe how I feel so many people worked to make the many months Charlie and I spent in hospital bearable.

I also want to thank the kind person who gave his Bone Marrow to Charlie and so gave him a chance of life. One day I hope to meet him to thank him and show him Charlie. Without the transplant I don't think Charlie would be here today.

KITS STORY

Kit was born with Hyper IgM or CD40 Ligand Deficiency. This is his story, written by his mum, Fiona.

In 1989 when he was ten months old, our son Kit was diagnosed with a Primary Immunodeficiency called Hyper IgM. This condition was thought to be an antibody deficiency although, for some reason not yet fully understood, people with Hyper IgM did less well than those with other antibody deficiencies. Over the next eight years Kit was treated with intravenous immunoglobulins, and apart from one or two episodes of neutropenia, he was fit and well, attending school, playing football, swimming, ski-ing and playing with his friends.

Since the gene for Hyper IgM was cloned in 1994, the nature of the condition has become clearer. Scientists found that it was a combined immunodeficiency with some T-cells missing. The condition was renamed CD40 Ligand deficiency. In 1996 an Italian immunologist, Dr Luigi Noterangelo, published his research into the condition. By constructing a register of these patients worldwide, he looked at why many of them did badly, often in the second decade of life. It appeared that many (80%) had significant liver problems by the time they were 20. It was thought that the origin of these liver problems was a common parasite - Cryptosporidium - that people with CD40 Ligand deficiency were unable to deal with. Because of our involvement with the PiA, my husband and I were at a meeting when this research was published and we were able to talk to many of the doctors and scientists in the forefront of this research. Some immunologists were suggesting that these patients should be considered for bone marrow transplant (BMT) and we discussed this option with the team at Great Ormond St Hospital for Children NHS Trust (GOS) who have looked after Kit all his life. In the summer of 1996 we found that we were one of the 25% of families who had a sibling match - our daughter Sarah's bone marrow was a match with Kit's. However, Kit was really well, his liver function tests were all normal, and he showed no sign of Cryptosporidiosis.

The team thought that we probably had time on our side - some new therapy might come along in time for Kit. In Gothenburg we had heard of recombinant CD40 Ligand therapy - a French immunologist had hopes of this being available in the next few years. In any case it seemed such a counter-intuitive thing to do - to take a child who is to all intents and purposes well and put him through such an invasive and potentially risky procedure as a bone marrow transplant. We decided to wait, and to act only if Kit's liver function tests started to show abnormalities.

Over the next few months 'the decision' was never far from our thoughts, and then a chance meeting with an eminent immunologist at a media 'Jeans for Genes' event started the discussion again. On being asked his view, he said that in his opinion the best time to do a bone marrow transplant is when the child is fit and well. He also felt that new therapies were still some years away. Then followed a series of discussions with immunologists and the BMT team at GOS. The decision focused on this issue: if we opt for a transplant and Kit dies, could we live with ourselves? Conversely, if we postpone and he becomes ill and then dies in transplant, can we live with knowing that we probably passed over his best chance of a cure? Although my husband, Chris, is a mathematician and found the statistical arguments overwhelmingly in favour of a transplant, we still found both issues were very difficult to address. We eventually concluded that Kit's chances of surviving a transplant were so much higher if he went into transplant fit and well. This option unquestionably gave him his best chance of a normal adult life. Having discussed all of this with Kit and his sisters, we decided to go ahead. The children all found the decision much easier than we did - to them it was obvious that Kit should have the transplant. As his mother, although I had made the decision with my head, with my heart I wanted to pick Kit up and run away with him to a remote place, where he would be safe from infection. The transplant date was fixed for October.

In mid-October Kit had a Hickman line put in, and a liver biopsy done. This was the first time GOS had done a transplant on a child with CD40L deficiency but other centres had found apparently well children had hidden liver problems. We were greatly relieved to hear the next day that his liver seemed to be fine. However, a few days later we were telephoned by one of the immunology team to say that the biopsy had been cultured and a bug was found. Not Cryptosporidium, as we had feared, but Microsporidium. To us it seemed that this both underlined the need for a transplant, but might make the transplant more risky. Although Microsporidium was thought to be less invasive than Cryptosporidium, its presence seemed to mean that, without a transplant, liver problems were on the cards for Kit. The presence of any bug before transplant increases the risks, as once the immune system is suppressed prior to transplant there is nothing to stop the bug multiplying. The final date for the transplant was fixed for the end of November and we went back to GOS on 17th November to begin chemotherapy. Kit was very matter of fact about the whole thing. He knew what would happen - he knew he would lose his hair

and so he had dyed it green and purple for his last days at school. The staff on the BMT unit are so totally child-centred and kind that he didn't dread his return to hospital at all.

For the first few days of chemotherapy he stayed well. We were not in isolation and so Kit could use the ward corridors to roller-blade, even when on a drip. He was a bit phased to find that he would be on a drip all of the time until 35 days after transplant. This was because the team knew his liver was vulnerable and wanted to lessen the risk of a complication of BMT that affects the liver, Venoal Occlusive Disease. They did this by attaching him to a Heparin drip from ten days before the transplant to 35 days afterwards. Transplant day was Friday, 28th November. The Sunday before, Kit and I moved into our isolation room. Kit would now not be allowed out of this room until his blood counts started to recover after the transplant. My husband and I spent the Sunday getting the room ready with all his belongings, posters, games and toys. The hospital provides about £30 worth of new toys for each child having a transplant. Kit and the play therapist had chosen these the previous week. Everything that goes into the room has to be new or nearly new, and has to be wiped with alcohol wipes, or washed and tumble dried. Kit roller-bladed all day, and in the evening was happy to roller-blade into his room. From now on, he would not be allowed to leave his room and only three family members: myself, my husband and my mother, were allowed in. Everyone entering the room had to scrub up and put on a plastic apron. In the room there is a fold-down bed for a parent. We had planned for my husband and I to take turns, but it quickly became clear that when he felt poorly, Kit wanted Mummy, and so I stayed with him throughout. The room also has a TV and video, and a bathroom.

The next day we started the second round of chemotherapy and we saw the first signs of the two complications that were to dog us throughout. The first was nausea and sickness, a common complication, especially with older children. The staff are very good at giving anti-sickness medicine, and for most children this works. It didn't for Kit and sickness was, for him, the worst part of the whole thing. The other complication for us was nose bleeds, often set off by vomiting. All his life Kit has had nose bleeds, and his doctors have assured us that this is nothing to do with his condition; he is just a kid who has nose bleeds. However, he was now on Heparin, his platelets were falling because of the chemotherapy and the nose bleeds were frequent and profuse. The BMT team suggested stopping the Heparin. However this worried my husband and I, as at that stage we were primarily concerned about his liver. After some discussion it was decided to keep him on Heparin, but keep his platelets high with platelet transfusions.

The day before the transplant our daughter Sarah, who is 17, was admitted to the ward. This was quite a high point for us all - Sarah's room was across the corridor from Kit's and she could talk to him on the intercom. The next day she went down to theatre early in the morning and was awake by lunch time ready to see the bag of her marrow (which looks like blood) being slowly infused into Kit. People told us they found transplant day an anticlimax, but for us the experience was deeply moving: watching something from one child go into another. Kit was fairly well on transplant day, although still nauseous. The next day Sarah was well enough to go home, and she was back at school within a week, although she still felt rather weak and wobbly for a few weeks.

This was a difficult time for the rest of the family at home, especially for our fourteen-year-old daughter Amy. Fortunately we had the support of all four grandparents (including my 90-year-old father, who with my mother moved from Scotland to stay in our house to be with the girls. They stayed for the duration - the longest time my father has ever been out of Scotland). Amy's vital involvement was still to come, but at the time of the transplant she inevitably felt left out.

Now the waiting started. After transplant it takes two to three weeks for the new marrow to engraft and start producing cells. During this time the child is totally immuno-compromised and feels totally flat. They are obviously very much at risk of infections. Our days and nights were totally taken up with a long round of intravenous drugs - antibiotics, blood products and drugs to protect Kit from Graft-vs-Host Disease (when the new cells attack the host, the host being the child having the transplant). He was soon unable to eat anything and after a disastrous try with a nasal-gastric feeding tube, which only served to worsen the nose bleeds, we went on to intravenous feeding via the

Hickman line. Most children need some form of artificial feeding during transplant, some, like Kit, because of nausea and sickness, some because of the sore mouths that are a common complication - we managed to avoid that. For the first two weeks Kit felt flat and nauseous but was progressing as planned. As throughout our stay, we were constantly busy. There is always something to do, from the four times daily mouth care - to prevent the painful mouth ulcers that occur with a lot of children - to the daily visits of the teacher and play therapist. However, 14 days after transplant, his temperature rose, and his liver, which had been slightly tender, began to really hurt. It became clear that there was something wrong with his liver, although he was not showing any signs of Venous

Occlusive Disease. A few days later he was found to be excreting Cryptosporidia. My husband and I remembered hearing an eminent French immunologist say that: "They (those with CD40L deficiency) all have Cryptosporidia somewhere, if you look hard enough." We had thought that Kit was the exception. He became very jaundiced and unwell. The next week was very worrying, and Kit felt very poorly.

It was now clear that engraftment of Sarah's marrow into Kit was taking place, as the daily blood counts were beginning to show some sign of activity. On the Thursday of that week we saw a neutrophil count, and by the weekend he had enough neutrophils to go onto 'yellow precautions', i.e. his sisters were allowed into the room and he could go out into the corridor when it was quiet. He was still very jaundiced and nauseous, and all of his liver function tests were considerably elevated. However when his sisters came into the room and started to play we saw the first smile since the transplant! The team thought that the blockage in his liver was caused either by the bugs or by the new cells coming in and attacking the weakest point in the body. Christmas Day was spent happily with all of the family in the corridor outside his room. The staff go to amazing lengths to make the day as happy as possible for all families, and Kit, thank goodness, was well enough to enjoy the day. He even ate a little Christmas dinner.

Gradually the liver function tests began to improve and the jaundice started to recede. Kit began to feel better, and enjoyed his daily visits from his sisters, who were on holiday from school. Every day he longed for their visits, and it was great to see that Amy's ability to make him laugh and get up to mischief was undiminished. This played an important part in his recovery.

Preparations started to get Kit ready to go home. First of all he had to take all of his medicines orally rather than through his Hickman line. This was quite a battle, as nausea and sickness were still a problem. Kit had gone into hospital able to swallow large tablets. Now the thought horrified him. Then we had to get the house ready - carpets cleaned and everything else as clean as we could. The dog was dispatched to stay with a friend for a few months, and the car valet cleaned. We came home on the 9th January. We left with overwhelming gratitude to the gifted staff of Robin Ward at GOS. Getting home was lovely, although daunting. It was a little like coming home with a new baby, only this baby talked! However, within hours of being home we had visits from the community paediatric nurse and our GP.

Kit is still on a lot of medication, nausea is still a problem and eating a bit of a battle, but he is now beginning to eat more normally and is gaining weight. It is still far too early to be complacent. At the time of writing it is only 76 days since the transplant and there are still many things that can go wrong. Did we make the right decision? Who can say, but having been through transplant we are sure that had we waited for the liver problems to show up, transplant would have been much rougher on Kit and more risky. It was hard enough and risky enough as it was. For us, the transplant would seem to have been 'just in time'.

Post script: This article was written originally for the PiA's magazine Insight. It is now nine months post-transplant and Kit has had an excellent summer. He went back to school after Easter, and, although he was still tired and had to come home early some days, he greatly enjoyed being back with all his pals and starting to play sport again. As far as school work is concerned, his progress does not seem to have been hampered much by his absence. He was very keen to re-join the school's cricket and ski-ing teams,

and managed to make the last ski race of the season (held on dry ski slopes). He fell and broke his arm. So no sport again, and his view of life plummeted. However once the arm recovered, we have all enjoyed a great summer. His T cell counts are rising and are now nearly in the normal range. He is still on intravenous immunoglobulin, but the period between infusions is gradually lengthening. He seems to have fully recovered his former stamina and general joie de vivre. He looks like himself again. Once he stopped taking Cyclosporin, his hair, which had grown back quite dark, gradually became blonde again (I know it shouldn't matter but I minded that he didn't look like the old Kit for a time.) BMT is a life altering experience for the whole family. We have been extraordinarily lucky - we had a sibling match, Kit was still fit enough for transplant, his recovery has been fairly straightforward. We can now look forward the possibility of Kit being cured. Having lived with what we thought would be a life long condition for 10 years, this is hard to imagine. We have been asked many times if the experience has changed us. One wise nurse at Great Ormond Street Hospital told Kit: "If you go through fire, you come out as steel," and in many ways we are stronger - Kit certainly has a maturity beyond his years. However, one thing that will stay with us all is the profound sadness at the deaths of other children that we came to know through Kit's transplant. We got to know some families through the PiA and, while we were in Great Ormond Street we got to know several families whose children were undergoing BMT for leukaemia. Some of these children died and the sadness at their families' loss will stay with us all for a long time.

We now look forward to 'normality', whatever that is! •

TANYA AND AISHA'S STORY

Tanya and Aisha were both born with Severe Combined Immune Deficiency. This is their story, written by their mum Aditi.

Tanya was born on the 1st December 1989 in New Delhi, India. She was our first child. I held her in my arms and she looked absolutely beautiful. The only things I thought were very strange were that she cried a lot, seemed to need a lot of comfort and had very cold feet that wouldn't get warm. She had her first live vaccine (BCG to prevent tuberculosis) at one month of age (all babies in India receive this vaccine as a matter of course) and from then on all her various medical problems began. At first she had recurrent oral thrush, then she developed a lump in her armpit and started to get a low-grade temperature in the evenings. Despite consulting with many different paediatricians - the five top names in New Delhi, the doctors recommended by my husband's firm, only one doctor made a passing comment on her immune system. She did not get well, and by now she was on oral medication for the tuberculosis caused by her immune system's inability to fight the live BCG vaccine.

The most frustrating thing was the attitude of the doctors; neither could they get her well nor would they admit that they did not really know what was going on. One doctor even wrote out a prescription for a tranquilliser for me and told me to stop taking her temperature! Tanya was finally admitted to hospital with a very high fever and the doctor suggested that she probably had a superimposed infection on the BCG site, which had started to ooze. He put her on intravenous antibiotics and then sent us home despite the fact that her fever had not subsided. A week later her fever spiked uncontrollably and the doctor suggested that we should consider removing the infected lymph node surgically. I insisted on yet another opinion and took her to a doctor who had international experience. He diagnosed her as having cell-mediated immunodeficiency. The family was by now in shock. She was re-admitted to hospital. On my insistence the doctor agreed to do more blood tests, however he went on to give Tanya a blood transfusion to boost her haemoglobin before the operation. He used non-irradiated blood. We now know that babies with Severe Combined Immune Deficiency who need blood transfusions need to receive blood which has been irradiated. Tanya reacted to the transfusion and developed Graft-vs-Host Disease. She died of this in July 1990.

I later learned that her symptoms of persistent oral thrush, over-reaction to BCG and Graft-vs-Host Disease from non-irritated blood were typical symptoms of the type of Severe Combined Immune Deficiency (SCID), when the child is born with a deficiency of both B-cells and T-cells. This is also known as 'Baby in the Bubble Syndrome'.

Our son Ishaan was born in 1991 and today he is a healthy six year old.

Aisha was born in March, 1996. When I noticed that her tongue was coated I panicked. Tanya had had a white patchy tongue, but Aisha's was a more even white coating. The doctors brushed it off as milk coating. She barely gained 450 grams in weight each month, compared to my son who used to put on at least 8-900 grams a month. Our doctor continued to assure me that I was panicking unnecessarily and I felt that I should believe him, especially since he had been the one to diagnose Tanya.

At four months old Aisha developed severe diarrhoea. She was put on antibiotics and recovered, only to get more diarrhoea three days later. It seemed to me that the whole story was beginning to repeat itself. Four antibiotic courses later I told my husband we should get another opinion from a gastro-enterologist. It was in that split second that I realised that she also had SCID. It seems that an intuitive feeling that something is wrong and that the doctors are not getting to the bottom of it is a common experience among SCID families.

The gastro-enterologist ordered T-cell, B-cell and immunoglobulin counts for her. The test results showed that she was making immunoglobulins, but had absolutely no T or B cells! The little knowledge we had gained about the immune system told us that this could not be, as we knew that it was the B-cells that produce immunoglobulins. Obviously one of the results was an error. We went back to the gastro-enterologist that had ordered the tests and he was not too happy to see us. He said, "I am out of my depth, there is nothing I can do to help you, my best advice to you would be to find an immunologist."

We went back to our paediatrician and he said much the same. So where was this immunologist we should be seeing? We were advised by our doctor to take Aisha abroad because there were no trained Paediatric Immunologists in India. Our Paediatrician told us that a bone marrow transplant was her only hope, or she would definitely die before her first birthday.

My husband sent faxes to France, Australia, U.S.A and England and we waited for a reply. We knew that transplants can cost anywhere between U.S.\$2-300,000. The only hospital to give us a quick reply was Great Ormond Street Hospital in London. I still bless Dr. Gerritsen each day for having given us such a kind and quick response. We arrived in London on the 5th August 1996. Of course the hospital wanted a deposit of £120,000 before commencing treatment, and told us they would need more if the money ran out. My husband decided that he would do his best to raise the funds. I had my hands full trying to keep Aisha as comfortable and protected as I could; she now had such severe diarrhoea that her rectum was cut and bleeding. She ran fevers of 106°F and she was having 20-25 motions a day. Since we couldn't afford to admit her to hospital I started to give her baths with tea-tree oil and used Sudocrem on her bottom. I was still breast-feeding her and I think that helped a lot. If I gave her jars of pre-prepared baby food, she passed them out absolutely undigested. I started to feed her powdered baby food made up with water. It took a month of trial and error and then, miracle of miracles, not only did she recover from the diarrhoea, but her bottom healed and she started to gain a little weight! However, Aisha's blood tests continued to show that she was not producing any B-cells or T-cells and had no immunoglobulins either. She was put on Septrin and subcutaneous immunoglobulin, which I learned to administer at home.

My husband, myself and our son had been tissue typed in India, but when my husband's tests were repeated here, some of the Indian results were found to be wrong. Our son had to be brought over from India and that set things back by 15 days. On re-testing Ishaan was found to be a 3/6 match, I was a 3/6 match also and my husband was a 4/6 match. The doctors decided to hunt for a better match for Aisha through the Anthony Nolan Trust. A month later the doctors told us that although they had seven preliminary

matches, none of them matched Aisha on further testing, so they would go ahead and give her my husband's marrow. This meant that she would be having a Haploidentical Transplant, which is a half-matched transplant. It was decided to also give Aisha a boost of stem cells from my husband. His production of stem cells would be boosted with injections of a drug called GCSF, given over several days, and then the stem cells would be harvested from his blood and given to Aisha.

Meanwhile my husband met with the owner of Sunrise Radio, the largest Indian radio station in the UK. He promised to help in whatever way he could. We now had a date for admission: 22nd October 1996. At the beginning of October, the radio station called to say that they had obtained clearance for Aisha's broadcast appeal. The response to the appeal was overwhelming; Sunrise Radio raised £273,000 for Aisha's treatment and the cheque was presented to the Chief Officer of Great Ormond Street Hospital just as Aisha was receiving her chemotherapy. We were overwhelmed by the generosity of the listeners to Sunrise who had made a miracle possible.

To minimise the risk of Graft-vs-Host Disease, some of the T-cells from my husband's marrow were removed before giving the marrow to Aisha. She was also given his specially harvested stem cells.

The transplant day arrived and it was a bit of an anti-climax, the marrow? just went into Aisha's Hickman-line, no cuts, no discomfort at all. I must admit I was more worried about Niren, who was in quite a bit of pain from the marrow extraction!

I knew that the worst of the side effects of chemotherapy were yet to come. Aisha was a little sick and her hair began to fall out, which was awful; when it came out in chunks in my hand my heart just bled. Her vomiting lasted about three days, but she had no sore bottom, no sore mouth and she began to tolerate the NG tube milk feeds well. She would also eat a little bit even if it was only a spoonful. Slowly her appetite returned. About 15 days post transplant her first few white cells showed up in the blood reports and another 20 days later her platelet counts began to rise as well. I had expected her to need TPN and morphine, but all she needed was platelets and red blood cells a couple of times. In herself she was happy, she contracted no other infections and was even gaining a little weight!

Aisha was discharged from hospital exactly 45 days from the day she had been admitted and to me that was a miracle, as I had expected to stay at least three to six months. In short, Aisha had a brilliant BMT.

I thought the worst was over. However, our problems started four months later when she developed severe diarrhoea and vomiting. This did not clear up and two months later, after a gut and skin biopsy, it was diagnosed as Graft-vs-Host Disease. She had been on Cyclosporin to suppress GVHD, however with such severe diarrhoea she had not been absorbing a sufficient dose. She was put on an increased dose of Cyclosporin and another steroid, Prednisolone. She immediately improved.

I took Aisha back to India eight months post transplant. There she developed necrotising entero-colitis, a severe infection and inflammation of the lining of the intestine. We rushed back to England for surgery. Due to this severe infection and the steroids to suppress GVHD, her immune system, which had started to develop, also suffered a setback. The doctors now felt that her recovery would be slow and that she may need treatment for another two years. My husband's company was very sympathetic and agreed to transfer him to the UK to facilitate the transition.

By God's grace, the help of our many friends (especially the Kamat family, who very generously took us and all our problems into their home and hearts), the facility of Great Ormond Street Hospital, and of course the generosity of the listeners of Sunrise Radio, Aisha is a very lively and happy two year old, who loves and lives life to the fullest. Her treatment is by no means over, but we can, at last, see the light at the end of the tunnel.

NICHOLAS' STORY

Nicholas was born with Hyper IgM (CD40Ligand deficiency). This is his story, written by his mum, Christine

Nicholas Steven Jowett arrived into the world via Bradford Royal Infirmary at 2.30pm on Sunday 3rd June 1984. He weighed a healthy 9lb 3oz and took to breast feeding easily. He was a bottle. Our routine at home was a normal one for a mother with a three year old (Andrew) and a young baby - visiting friends, going to playgroup, visiting the park; and on this regime Nicholas was gaining weight, sleeping well, meeting the milestones of sitting and generally thriving.

After a family holiday when Nicholas was three months old his routine changed. No longer did my little baby settle for the night. He was waking and crying. It was clear it was not hunger, but I was worried that something had changed.

I was lucky, our family GP felt that a mother's instinct was generally right and he listened attentively to me and carefully examined Nicholas. I was reassured but not dismissed. As the weeks passed Nicholas was prescribed antibiotics, initially for ear infections. The first inkling we had of the times ahead was that these were not clearing up as quickly as we were given to believe.

Although Nicholas was restless at night, at this stage he was still a happy baby during the day and enjoying changing into a mixed feeding regime. Gradually he became increasingly sleepy in the day and it was hard to feed him either solids or milk.

Before Nicholas' first Christmas I was alarmed to notice that his chest was sucking in on inspiration (which is a sign of a serious chest infection in a baby). He was admitted to St Luke's Hospital, Bradford. There was a lot of mucous and the doctors suspected cystic fibrosis: the tests came back negative. It was clear that the hospital were taking us seriously as we were being asked about our families health histories. Nicholas' first chest x-ray showed a lot of infection and now the diagnosis changed to pneumonia. He was treated with intravenous antibiotics and physiotherapy.

By January, a month after his treatment began, Nicholas' pneumonia had not cleared up. It was an enormous strain on the family keeping my two young sons attended to. On one particular day when I was sitting with Nicholas, the nurse asked when my husband, Alex, was coming as the doctors needed to speak to us both. Having summoned Alex from work we were told that Nicholas had Hypogammaglobulinaemia; that our baby boy didn't have a normal immune system and that he would need some treatment for the rest of his life. Clearly this was a rare condition because they had not come across it before. We were told that Nicholas would need weekly intra-muscular immunoglobulin injections, and it became painfully obvious that we had a sick child on our hands. This came as an enormous shock to us, as both sides of our family have always enjoyed rude health.

Straight away, even at seven and a half months of age, it was clear that Nicholas had a very high pain threshold as these injections were very thick and took a long while to enter his buttock.

All the family were ordered to have blood tests, to see if any of us had signs of Nicholas' illness; we all had a clean bill of health. Nicholas began to thrive again thanks to the immunoglobulin injections.

In March 1986 when Nicholas was two and three quarters years old, he caught a barking cough which developed into croup. The staff at St Luke's Hospital were confident they could treat this with steam and that it would be unlikely he would need oxygen. However, the outcome was so severe that Nicholas was transferred to the Bradford Royal Infirmary where he was placed on a ventilator in their intensive care unit. There was one awful moment where the ventilator broke down and we were pushed into the corridor fearing the very worst. Nicholas, however made a full recovery and learnt at this tender age to get the most out of the situation by asking for sweets.

For years Nicholas was plagued by mouth ulcers - a result of antibiotic treatment and a side effect of Neutropenia. At this stage Nicholas was not underweight, and whilst we were concerned at the amount of discomfort the ulcers gave him, they did not seem to nutritionally compromise him. Up to starting school, Nicholas was on weekly immunoglobulins and occasional antibiotics but managed to thrive none the less.

In September 1988 Nicholas started school. He could already read and had begun playing the piano. Whilst at infant school it became apparent that arithmetic was going to be his forte. Nicholas became firm friends with Oliver, another bright and sporty child. They shared many games together, including formal sports, Ghost Busters and Ninja Turtles. Unfortunately as Nicholas' illness took hold, Oliver left him behind on the sports field but not academically. Nicholas had his share of knocks and scrapes in the school yard, went swimming, played the piano, joined Beavers (and later Cubs), went to Sunday School and took a keen interest in cricket and football. It was suggested that an immunologist rather than a paediatrician should take over Nicholas' care. We were fortunate enough to meet Dr Gooi, based at St James' Hospital in Leeds. In December 1990 Nicholas started having monthly intravenous immunoglobulin infusions (instead of having weekly intra-muscular immunoglobulins: the idea was to give him more at one go and thus keep his immune system functioning at a higher level). Initially this was done in hospital with the aim of us being able to administer it ourselves at home, but in the end it was always a hospital visit.

In August 1991, our summer holiday in the Isle of Wight was spoiled for Nicholas by an enormous mouth ulcer. It covered the whole of his bottom inside lip. On our return Nicholas was admitted to Seacroft Hospital. At this point G-CSF was used intermittently (G-CSF is given to increase Neutrophil production). This treatment was very successful for Nicholas.

It was in November 1991 that we first heard the word *Cryptosporidium*. Nicholas and I both had severe diarrhoea. In my case it was over in 48 hours, but Nicholas continued with this problem, so the whole family were tested. It turned out that both Nicholas and I had *Cryptosporidium* in our systems. As a healthy person myself, I was able to free myself from *Cryptosporidium*, but for someone with a compromised immune system this meant trouble. But of course at this time we did not realise the severity of it.

I would like to state now that it is my view that anyone with a severely compromised immune system should drink only water that has been boiled. (Editor's note: the advice of the Medical Panel of the PiA is that anyone with severely compromised T-cells should drink only water that has been boiled). I believe that this information could have saved Nicholas' life. There is no known cure for *Cryptosporidia*.

For Nicholas, *Cryptosporidiosis* meant that he ceased to thrive. From the age of seven it was as much as we (parents and doctors) could do to maintain his height and weight level. From that point onwards Nicholas' appetite was poor, he had constant diarrhoea and was intermittently sick. The illness was symptomatically controlled with different antibiotics and anti-*Cryptosporidial* treatments. However his symptoms waxed and waned a lot and he was started on Lactobin (this was horrendous - it was in half pint doses, five times a day, supposedly to be drunk at an optimal temperature; clearly it nauseated poor Nicholas and often induced vomiting). He had two courses of Lactobin but still signs of *Cryptosporidia* were there.

We were told in December 1993, two years after he first had *Cryptosporidiosis* that, despite the potassium supplementation, vitamins, minerals, various antibiotics and gamma interferon (to boost the immune system), unless he *Cryptosporidium* could be cleared from Nicholas' body, he would die. A lot of treatments had been tried and hope was placed in a new one called PEG IL2 (from America). But this did nothing to alleviate the situation, causing even more virulent diarrhoea and vomiting and eventually had to be stopped.

How do you encourage a child with a poor appetite to eat? The smallest meal made him 'feel stuffed', 'feel sick' or cause him to vomit. We were painfully aware of how thin and how small he was. As milk is supposed to make bugs in the gut multiply we were advised

to totally avoid it. Ironically, a few of the things he could actually stomach such as breakfast cereals, Angel Delight, ice cream etc. were now off his diet. As it turned out, avoiding milk did not seem to make any difference to how Nicholas was, and he was gradually introduced back onto it.

It was at this point we went to Great Ormond Street to see if their expertise could help Nicholas. There he was subjected to a liver biopsy, a colonoscopy and endoscopy. Nicholas was now diagnosed as having Hyper IgM, which at the time meant very little to us. All we were told was that the difference between Common Variable Immunodeficiency and Hyper IgM is that Hyper IgM sufferers are prone to Cryptosporidia.

Back to St James' Hospital, Leeds, where we began tube feeding, overnight, through a nasal gastric tube. This we did at home sporadically with a degree of frustration on our part as despite Nicholas' co-operation, clearly this feed was not tolerated. This went on for the next couple of years.

Nicholas started at our local middle school in West Yorkshire in September 1993. At the end of his first year there he received a prestigious award - The Raymond Derrick Trophy for Academic Excellence. The head teacher was later to say in his eulogy: "This was a tribute to Nicholas' hard work and commitment to his learning. It was clear to his teachers that Nicholas was a bright, talented and hardworking pupil."

Whilst at the middle school he built a close circle of friends - Oliver moved up with him and Thomas and Michael joined the pair. All four were known for their competitiveness, both in lessons and in sports but as the term progressed Nicholas simply did not have the energy to run around. Nicholas was especially known for his good sense of humour. He developed a prowess for chess, joined, and later helped run the school bank. He began to get involved in local cricket clubs, especially Harden and Wilsden. If he wasn't well enough to play, he was keen to do the scoring. He liked the atmosphere, the maths, working out everybody's averages, and, during matches, informing the players how many runs per over were needed to win the game, and of course he was grateful to be earning some money. He did this not only for the under 12's (the team he desperately wanted to play in), but also the under 15's (which Andrew played in) and his Dad's cricket team.

In December 1994, Nicholas managed to contract Salmonella. He began to dehydrate rapidly. The stools were weighed and, in theory, this was replaced by a hydrating solution. Overnight Nicholas lost so much that each morning he looked sunken-eyed and shrivelled. At this point he had to stop eating and had a permanent tube for elemental feeds. At one stage it was hoped that the Salmonella might drive the Cryptosporidia out of Nicholas' system, but unfortunately it didn't. Eventually Nicholas began to put on some weight and gradually he was weaned off the supplementary feeds. But although we had managed to eradicate the Salmonella we were still stuck with the Cryptosporidium and things went back to how they'd been before.

In desperation we turned to alternative methods - healing, and later homeopathy. At first he did well on that but as the illness marched on it could not be contained - Later on we tried acupuncture, but that never touched his condition. We also tried aloe vera, live yoghurt, acidophilus tablets, Bach flower and herbal remedies.

The timing of the Salmonella meant we couldn't go back to GOS and as things turned out we were never to go back there again. Salmonella had certainly added to Nicholas' existing health problems - for almost half a year he was too poorly to attend school and hence had home tutoring. The next half year we spent building him up so that he could gradually return to full-time education. His illness caused us to have many broken nights but he bore this stoically and none of his friends were aware of how much he was suffering. Despite persistent low energy levels he maintained his position in the top stream for all his academic subjects and did indeed play some cricket whenever he possibly could.

Basically 1995 whilst getting rid of the Salmonella and all the problems that it brought, was spent getting Nicholas in reasonable health by the following anniversary of the attack.

The start of the National Lottery brought new hobbies for Nicholas: with his love of numbers he spent hours (often sat on a hospital bed) working out statistically which numbers were likely to come up, likewise studying the form for horse racing, in fact anything to do with figures and Nicholas was keen to fathom all the different permutations. Windows 95 and later the Internet proved invaluable distractions for Nicholas.

We were always busy in 1996 going back and forth to St James' for various infusions and consultation (with Dr Gooi and Dr McClean) and once again we were finding it increasingly difficult to maintain his weight. Nicholas was very keen to go on a school trip to France: it was touch-and-go right up to the very last minute whether he would make it. He did – I accompanied him and tried to blend in by helping with all the children. In fact on the outward journey many of the children were sea-sick, but this was nothing new to Nicholas, he was used to it. At no time did Nicholas wish to be seen as different from his peer group. It was important to him to be treated just like the other pupils – it earned him the respect of both his own friends and his teachers. Nicholas really enjoyed his trip to Brittany and being part of the class he loved. Twenty four hours after returning home he was back in St James' hospital covered in a rash with a rattly chest, a sore mouth and once again low in albumin.

After Dr Gooi returned from the IPOPI conference in Sweden, he came straight to see us. Hyper IgM had been on the agenda and it was being seriously considered whether bone marrow transplants and/or liver transplants could be curative. Dr Gooi approached us asking us to consider whether a BMT would be an acceptable way forward for Nicholas. Naturally at first we were horrified at the prospect. But the reality was that the future forecast for most Hyper IgM sufferers was bleak without one. Even though the entire family was in shock at such a drastic measure being called for, the immediate family was tested as to suitability to donate bone marrow: luckily his brother turned out to be a perfect match.

Dr Gooi knew of the work of Dr Andrew Cant, an immunologist who specialised in BMT for immunodeficiencies. We were invited to meet him at Newcastle General Hospital. In August 1996, Alex and I, with Nicholas went there for six days worth of tests. From the results they ascertained that he was a suitable candidate for BMT Whilst we wanted him to be suitable, ironically when we were told that he was, our anxiety levels rose. Nicholas in contrast took a very matter of fact view. In October 1996, the hospital gave the go ahead for the BMT. It was now up to us to go along with the process - or not. We didn't really have any choice. The admission was planned for January 1997.

As Nicholas was poorly over Christmas he was admitted to St James' on New Years Day 1997. His weight was very low and he was very chesty; a Hickman line was inserted earlier than planned so that Total Parental Nutrition (TPN) could be started, hopefully to build him up before his transplant.

It was on Sunday 2nd February that we drove to Newcastle. The day before that he saw all his family and many friends and was given various presents, including an England football shirt from his class.

We had a week on a paediatric ward during which Nicholas' regime was started, prior to being in isolation. Since Christmas, Nicholas had been suffering for the first time with actual pain. He was in agony with stomach ache, Pethaedine only seemed to take the edge off it, making him woozy.

Whilst on the paediatric ward, Nicholas proudly wore his new England football shirt almost constantly. He understood that all clothing that was to be worn in the isolation cubicle had to be laundered at 60 degrees. Nicholas was adamant that it was not going to get spoilt in the wash and therefore he would not be wearing it. The first week in

Newcastle was a very emotional one for me. I'd gone on my own, and during the journey I felt that I would have loved to have disappeared with him, literally to run away. But my own logic told me that we had no choice, we had to go through with it. The weekend before Nicholas was to be moved from the ward to isolation, Alex and Andrew drove up to join us. We crammed into that weekend as much as possible, visiting Beamish village, Hadrian's Wall, MetroLand and Whitley Bay. On the Monday morning (10th February) just before going into his cubicle Nicholas took a bath. He started crying and asked me: "How long do cats live?" as he was worried that our two cats would die before he got home. (We had no pets when Nicholas and I got Cryptosporidium).

There were seven isolation cubicles on ward 23. Each one had a semi-clean and a sterile area marked by a red line. It was about 6ft by 8ft and in Nicholas' case it contained a bed, a locker, a chair, a medical cabinet and a commode. To get into the semi-sterile area one had to wash your hands, but to cross the red line one had to 'scrub down' and put on a clean hat, gown and apron. Nicholas was confined to the sterile area. He was a stickler for the hospital rules - he would have told the top consultant if he had erred. Everything that went into the cubicle had to be sterile: if something was dropped on the floor it had to go out for re-sterilising. No one was allowed to sleep with their child (the hospital provides flats) and as our faces were considered non-sterile we could not kiss him. It was the parents responsibility to clean the cubicle by swabbing the surfaces with sterile wipes and mop the floor. No-one having a BMT ever feels hungry, and of course Nicholas never did have much of an appetite, so hence the TPN continued.

Cricket had played a large part in all our lives and this year Alex had been nominated for captain of Wilsden Cricket Club. Alex said to Nicholas that while he was in hospital he would not play. In response Nicholas said that he wanted him to play on Saturdays and then come up on Sundays to tell him all about it.

Chemotherapy started straight away, getting increasingly potent. Nicholas unfortunately was used to vomiting, so this was nothing new.

On Wednesday 19th February Andrew went into Freeman's Hospital, Newcastle for a general anaesthetic to donate his bone marrow. A few hours later it was slowly infused into Nicholas. For most of the time it was going on Nicholas had a nose bleed and at one point got upset because he thought he was losing it all. This was the first of many nose bleeds to come. Andrew was discharged the next day and went straight into see Nicholas, feeling pleased with himself. He was back at school the following Monday, having missed none to his annoyance, as it had fallen on half term.

The Cheltenham Festival of Racing was on at this time, and although feeling poorly Nicholas managed to read The

Sporting Life, either photocopied or taped to the outside of the window. He even managed to pick some winners. The nose bleeds continued, each one taking several hours to abate. Pressure treatment did not work, nor packing, but eventually, under general anaesthetic (within the cubicle), cauterisation did work, but Nicholas had huge clots of blood up his nose and in his throat which needed suctioning out many times daily.

From our point of view it seemed that Nicholas' bilirubin levels were a firm indication of how well he was doing. Someone would tell us his exact reading as we came onto the ward for the day and we became acutely aware of our son's toxicity and how yellow he was. It also became increasingly apparent that his awful stomach pain was caused by his liver.

We were delighted to find out that Nicholas' white cells were on the increase. The doctors knew that the bone marrow graft had fully taken, as all the peripheral white cells showed Andrew's genetic characteristics. We hoped now that the dreadful Cryptosporidium could be cast forth from Nicholas' body.

They are still wondering, given the timing of Nicholas' liver failure, whether his newly found immune system reacted to the massive load of Cryptosporidium, causing his liver to fail.

Nicholas died 34 days (25th March 1997, our 19th wedding anniversary) after his bone marrow transplant. The conclusion on Nicholas' post-mortem reads as follows: - "12 year old boy dying of multi-organ failure following liver failure. The liver failure caused by a combination on veno-occlusive disease (which may be related to treatment, in particular pre-bone marrow transplant conditioning and sclerosing cholangitis with Cryptosporidiosis (secondary to Hyper IgM syndrome)."

I wish the bone marrow transplant had been done years ago, before Nicholas contracted Cryptosporidium; after all, Andrew had always been a perfect match.

PREPARING FOR BONE MARROW TRANSPLANTATION

by Judith Armstrong, the Bone Marrow Transplant Nurse Co-ordinator at Great Ormond Street Hospital.

The following information explores bone marrow transplantation, and many of the questions frequently asked by families and children who are considering this as a possible treatment.

The decision to transplant

Bone marrow transplantation is a complex, high-risk treatment which makes huge demands on the patient and their carers. The decision to go ahead with a transplant must be made with the knowledge that it offers the best possibility of a cure but also that the treatment can fail and even be fatal. Your doctors will explain to you the side effects and potential risks of treatment as well as the potential benefit in order to help you make a well informed decision for your child. The transplant centre will also want to meet your child, to ensure that he/she has an age appropriate understanding of what the treatment will involve, and also to include her/him in the decision making process. At a later stage, a clinical nurse specialist, social worker, psychologist, doctor or counsellor will arrange to meet with you and tell you more about bone marrow transplants. These sessions are good opportunities for you to ask more questions and to discuss particular concerns. As part of your child and family's preparation for bone marrow transplantation, written information, audio tapes or videos, some of which should be age appropriate for your child should also be available from your transplant centre.

Finding a donor

The best donor for bone marrow transplantation, is a matched sibling (brother or sister) or other family member. This is because such an individual has inherited an identical tissue type to the patient, which allows the bone marrow to be transplanted with a lower risk of any reaction occurring between the recipient and the donor. In the absence of a matched family member, it is usually possible to find an unrelated donor from one of the worldwide panels.

Who should be tissue typed?

At most centres, the patient and the immediate family are tissue typed first. Each child will randomly inherit one of four possible tissue type combinations from the same parents. In searching for a potential bone marrow donor, each full sibling (brother or sister) has a 25% chance of being compatible with another.

What does tissue typing involve?

Tissue typing involves taking a blood sample from the patient and any potential donor. From the blood, it is possible to identify if the potential donor's bone marrow is the same as your child's. This is a complex test which may take a week or more before you are given results. Your transplant centre will be able to advise you regarding the length of time which you will have to wait.

Is it possible that a parent will match?

This is possible, however it is unlikely. Both parents would have to share similar tissue types in order for their child to inherit an identical tissue type to either parent. This can occur if both parents share a tissue type which may be common within the general population, or if there is consanguinity within the family, e.g. the parents are cousins or both families are related in some other way.

Could there be a potential match within the extended family?

An extended family search looks among other relatives and may be carried out if a suitable sibling donor is not available. Your transplant centre may ask you questions about your family tree and will give advice as to whether an extended family search is appropriate. To carry out an extended family search randomly without a proven indication

can be fruitless and can give false hope of finding a donor. Each transplant centre has its own policy with regards to searches of this nature, however, the following points may be useful indications for carrying out an extended family search:

- If both parents share similar tissue types
- If there is known consanguinity within the family e.g. both parents/families are related
- If the family originates from a country with a small non-immigrant population

What happens if a suitable potential donor is not identified within my family?

Your transplant centre will search for an unrelated volunteer donor whose bone marrow is compatible with your child's. Within the UK, there is an organisation called the Anthony Nolan Bone Marrow Trust, which is a charity-based organisation that has a registry of tissue types from volunteers within the general population. There are additional registries in the UK, based in Bristol and Wales and many others overseas, with the total number of donors now in excess of four million. Additionally, there are cord blood banks situated within the UK and overseas which are searched as donated umbilical cord blood is an alternative source of stem cells.

Your child's tissue type is sent to each registry. On identification of a volunteer who may match your child, additional blood is requested from the potential donor to confirm their tissue type. Identifying a potential compatible bone marrow donor for your child may take time which can cause anxiety, particularly if an unrelated donor search is necessary. Your transplant centre understands this and will endeavour to keep you informed as to what progress has been made and will do their best to identify a donor as quickly as possible.

Is an unrelated volunteer donor always found?

It is usually possible to find a donor for Caucasian patients. Children from ethnic minorities within the UK e.g. Mediterranean, Eastern Europe, African, African-Caribbean, Asian, Chinese or from a mixed ethnic background, may have difficulty in finding a compatible, unrelated donor. The donor panel registries are based mainly in UK, Europe, USA Canada and Australia, with smaller registries developing in other countries. Due to the location of these registries recruitment of Caucasian volunteer donors outnumbers those from ethnic minority groups. In this situation some families appeal for volunteers from their own ethnic background to come forward to be tissue typed. This is hard work with no assurance of success. It is unlikely that your hospital will be able fund or organise this but they can advise you as to where you can find help.

What does donation of bone marrow involve for the donor?

On identifying a suitable donor, he/she will undergo a medical examination. This is carried out to ensure that the volunteer is fit to donate and also to ensure that their donation causes no harm to your child. The donor undergoes the same stringent tests as a blood donor, including screening for infectious viruses such as hepatitis and HIV.

How is the bone marrow removed?

The donor will be admitted to hospital, generally for one night. He or she will receive a general anaesthetic and the bone marrow which looks like blood, is withdrawn from the hip bones using a syringe and needle. The marrow taken will replace itself naturally very quickly. As the donor will receive a general anaesthetic, no pain will occur during the actual procedure. However, the donor may experience some tenderness around the lower where the marrow has been taken from. General weakness and tiredness is expected for

a few days afterwards. Adult donors are advised to take a week off work and children some time off school.

What are the risks for the donor?

Because the donor requires a general anaesthetic, there is a small risk, as there would be with any other procedure involving anaesthesia. It is a minor operation and the donor will receive a full medical examination before the procedure to ensure that they are fit to undergo a general anaesthetic.

Sibling (brother or sister) donors

If a brother or sister is found to be a potential bone marrow donor, there are sensitive issues that you may find useful to discuss with your transplant centre. Care needs to be taken when discussing tissue typing results with your children. Many siblings, if found to have compatible bone marrow, take great pride and pleasure in being able to help their brother or sister in this very special way. Others may feel extremely alarmed at the prospect, but sense an expectation of what is required by their family. The remaining siblings in your family may feel disappointed at having lost out on their opportunity to donate bone marrow. Before the bloods are taken for tissue typing, or the results are known it may be useful to discuss with each of your children how they might feel if asked to give bone marrow to their brother or sister. This will encourage questions and could be a good opportunity to identify any fears or worries at an early stage. It is important that everyone is included in the preparations and discussions prior to admission for bone marrow donation and transplant, both at home and in hospital. It can also help, if each child is given his/her own specific role which contributes towards caring for their brother or sister. A common fear is that, if the transplant is unsuccessful, the bone marrow donor may blame themselves. There needs to be an understanding and belief that giving bone marrow is one component of a large, complex process. The donor is not responsible for the outcome of his brother or sister's treatment. Age appropriate, honest information should be given in a sensitive manner and your transplant centre can assist you with this. Picture stories, books about hospitalisation, time to listen and answer questions, visits to the transplant centre are all useful in helping your child who is to be the donor, and other siblings understand the process.

Unrelated donors

If an unrelated donor is chosen, great care is taken to protect you and your child's anonymity as well as the donor's. Some recipients and donors do meet at a much later stage upon request of the recipient and their family and also at the discretion of the transplant centre and the donor panel. Anonymous cards or a small gift can be sent to the donor via your transplant centre. This gesture is often greatly appreciated by the donor.

PREPARING FOR TRANSPLANT

How will my child receive chemotherapy, blood products and the bone marrow?

Your child will have a central venous line, often referred to as a Hickman line, which is inserted into a large vein under a general anaesthetic. Chemotherapy, blood products, drugs including antibiotics, nutrition, hydration, and even the actual bone marrow are all given through this line which is also used for blood sampling. This means that your child will no longer have to cope with needles. The central line is a thin, light silicone tube which exits onto the chest once it has been threaded through a large vein. Following insertion, the area around the line may feel slightly sensitive but this soon wears off. The line will not affect your child's mobility nor restrict the types of clothing he/she can wear. A dressing covers the line to protect and keep it secure. Baths are allowed, but your child will be discouraged from getting the line wet. Most children return home with the central line as often it is still useful at the time of discharge from hospital. Generally families cope well at home, looking after a child who has a central line. You will be given the necessary training and information to help you manage. The line is removed under a general anaesthetic once it is no longer needed. This may be any time from approximately 4-12 months after the transplant.

Chemotherapy

Once your child is in hospital, prior to receiving new bone marrow he/she will be given cytotoxic chemotherapy drugs. Chemotherapy is a necessary part of the process in preparing the body to accept new bone marrow. The function of chemotherapy is to destroy the defective bone marrow, including the stem cells. The combination and amount of chemotherapy drugs that your child will receive, will depend on his/her initial diagnosis and the type of bone marrow transplant which he/she is to receive. Your child may receive chemotherapy for up to 12 days before receiving the new bone marrow. Unfortunately there are a number of side effects which cannot be avoided and which may cause your child to become extremely unwell.

What are the common problems in association with chemotherapy?

Nausea and vomiting

Nausea and vomiting are frequent problems which are worst during the initial phase of chemotherapy. This may continue at intervals throughout the transplant period due to antibiotics or infection. Anti sickness drugs will be given regularly to your child in order to reduce this symptom as much as possible.

Stomatitis and Mucositis

Stomatitis is ulceration of the oral mucosa (lining of the mouth) and is a direct side effect of chemotherapy. A sore mouth can be extremely painful, resulting in your child not wanting to eat, drink, swallow or speak.

The mucous membrane also lines the entire gastro intestinal tract where ulceration can also occur, referred to as Mucositis. This can result in abdominal cramps and diarrhoea.

Not all children suffer from the above side effects and the severity of symptoms varies considerably.

If your child experiences these symptoms, he/she will lose their appetite and may lose weight. Pain relief will be given as well as necessary intravenous nutrients and fluids. As the mouth and gut heals, your child's appetite will improve and gradually they will be encouraged to eat or drink again. Chemotherapy may also cause altered taste but this problem will slowly resolve.

Bruising and bleeding

When platelets are low, symptoms such as nose bleeds are common and your child will also bruise easily. To minimise these symptoms, it will be necessary to give platelet transfusions intravenously until the new bone marrow starts to produce its own platelets. Early on, this may be as often as every two days and even when your child returns home, they may still require platelet transfusions at your local hospital. Eventually, this will become unnecessary as the new marrow will produce an adequate number of platelets.

Anaemia

Until the new bone marrow starts to produce its own red blood cells, your child will receive regular blood transfusions, to prevent anaemia.

Hair loss

Hair loss gradually occurs about seven to ten days after the last dose of chemotherapy over a period of three to seven days, and it can be irritating if it gets into the eyes and mouth. If your child has long hair, suggest having it gradually cut shorter before coming into hospital. This may help your child adjust to his/her hair loss and it may also help to minimise any discomfort. It is important to warn your child that they will lose their hair and also to reassure them that following the transplant, hair does grow back. Occasionally, it will return a slightly different texture or colour. If your child wishes, your transplant centre can organise a wig, although most children choose to wear a variety of hats or baseball caps.

Infection

Once the chemotherapy has destroyed the unhealthy bone marrow, your child will become extremely susceptible to infection until the stem cells in the new bone marrow produce new white blood cells. This can take between three to five weeks to happen. During this period, your child will be protected from infection, but any sign of infection will be immediately treated with intravenous antibiotics.

How will my child be monitored and protected from infection?

Specially trained nursing staff on the transplant unit will generally observe your child, including taking his/her temperature and blood pressure throughout the day and night. Nose and throat swabs will also be regularly carried out as well as collecting blood, urine and stool samples in an attempt to identify any infection which needs treatment. This constant around the clock surveillance may feel intrusive and disruptive to you and your child, especially during the night. However, it is a crucial measure as any infection in an immuno-compromised child can lead to a critical situation if undetected and left untreated.

Protection from infection

To help protect and prevent your child from acquiring infections, specific antibiotics and anti fungal medicines will be given to your child at the start of chemotherapy. These medicines are referred to as prophylactic drugs and your child will continue on these for a period of time once home, following the transplant.

During the period of time when your child is at their most prone to infection, he/she will be transferred into their own room to minimise contact with people other than those crucial to his/her care. Restricting social contact helps to minimise the risk of infection being spread to your child from other people. Many centres refer to this as the 'isolation period' and to your child's room as an 'isolation room'. These terms are slightly misleading, but please do not be alarmed. The following section aims to explore what the 'isolation period' will involve for you, your child and family.

What is an isolation room?

This is an every day room within the transplant unit which may have filtered air. The room is not sterile, but will have been thoroughly cleaned, especially for your child. When your child is at their most susceptible to infection, towards the end stage of the course of chemotherapy, he/she will be transferred to this room and will remain there for up to three to five weeks, or until the new bone marrow starts to produce white blood cells which will protect him/her from infection.

Who is allowed into the isolation room?

Most transplant centres will restrict your child's daily contact with persons other than parents, guardians, hospital staff and carers. Visitors are also restricted, including children.

Will I have to wear special clothing?

Different transplant centres will give different recommendations. Most centres will provide you with plastic aprons or cotton gowns to wear over your own clean clothes. Some centres may also ask you not to wear hand or wrist jewellery which can be difficult to clean. The most important and simple precaution is thorough and frequent hand washing whilst looking after your child.

What happens if I become unwell during the isolation period?

During isolation, your child is susceptible to infections which could make them unwell. Anyone who has been in contact with chicken pox, shingles or measles and has not had any of these diseases themselves should not come into contact with your child. Anyone

with signs of illness, such as high temperature, coughs, colds, diarrhoea, vomiting, conjunctivitis (red sore eyes), or a cold sore should also not have contact with your child.

As your child's carer, it is very important that you eat properly, take breaks, get sleep and fresh air in order to stay as fit and well as possible. If you do suspect that you are becoming unwell, please let staff know on the unit as soon as possible and they will advise you as to the most appropriate action.

What can I take into the isolation room?

Again, each centre differs slightly, but will advise you before your child's admission as to what is allowed. Generally, most items are allowed into the room as long as they have had minimal handling, are new or washable.

Despite some restrictions, the room will become you and your child's home for several weeks, therefore it is important to bring some familiar items e.g. photographs, pictures, books, which will help to make it 'your own'.

Will I be able to stay with my child?

Children's hospitals do not have restricted visiting hours. Your transplant centre will actively encourage you to stay with your child and to be involved in their care. However, it is important that you take frequent breaks. Most hospitals only have enough facilities for one parent to stay overnight, but you may wish to discuss alternating this arrangement with your partner or a relative or friend that your child is comfortable with.

How involved will I be in caring for my child?

You and your child will need the expertise, information and advice of the transplant centre. However, as a primary carer, your child will need you. Staff on the transplant unit will support and advise you regarding how to meet the basic needs of your child and will help you to continue to parent your child. Your role will be vital.

TRANSPLANT DAY

Your child will receive the new bone marrow after all the chemotherapy has been given. The bone marrow is given intravenously, into the central line, over approximately two hours and is similar to receiving a blood transfusion. Whilst receiving the bone marrow, your child will be monitored for any reactions but normally the procedure is straightforward and uneventful. Whilst the transfusion is in progress, your child may want to play games, read, watch TV or just sleep. Some families like to take photographs or even video the event, particular if a brother or sister has been the donor.

How will I know when the new bone marrow is working?

Following the transplant, blood samples will be taken from your child daily, to show the number of red blood cells, platelets and neutrophils being produced by the stem cells in the new bone marrow. During the first two to three weeks following the transplant, these cells will remain extremely low. As the new bone marrow begins to grow and function and produce blood cells of its own, the levels of red blood cells, platelets and white blood cells in the blood will increase. At this stage, a blood test is carried out to confirm that the new blood cells are being produced by the donor bone marrow. This test is referred to as 'engraftment studies' and will indicate that the new bone marrow has begun to function.

When will my child be better?

It may take one to two years for full immunity to return. Each child is different and your transplant centre will continue to monitor your child's immunity once you have returned home. Depending on the type of transplant that your child has received, within three to four months after the transplant has taken place, he/she may have adequate immunity to allow infection precautions to relax. At six to eight months post-transplant, your child

may have returned to school and the acute stage of treatment for most children and their carers is behind them.

AFTER THE TRANSPLANT: RESTORATION AND RECOVERY

by Rebekah Lwin, Clinical Psychologist attached to the BMT unit at Great Ormond Street Hospital.

In making the decision to proceed with bone marrow transplant (BMT) concerns are often focused, understandably, on preparations for the hospital admission and the transplant itself. These are seen as the areas that need the most immediate and critical attention and the greatest family adjustment. As a consequence, the personal, social and professional resources that may be required after BMT may often be overlooked, yet this too can be a difficult and psychologically stressful period which can benefit from early consideration and preparation.

It can be helpful to think about BMT as a process of discrete stages, each raising different concerns and drawing on different personal resources and coping skills:

Stage 1: Pre-bone marrow transplant - decision making and preparation

Stage 2: Hospital admission - separation, isolation and the BMT

Stage 3: Discharge - leaving hospital, early recovery and family re-adjustment

Stage 4: Long term adaptation

In our experience most families generally cope and cope well with the hospital admission period. It is difficult, tiring, distressing, demanding but the schedule is well structured and time limited. This stage is planned in careful detail by hospital and family and is usually well supported by extended family, friends and employers. Discharge from hospital comes after a hospital period of six to eight weeks, or longer for some children, and news of the discharge date is greeted with relief excitement, a flurry of domestic activity (generally cleaning and adding the finishing touches to recent home improvements) but also some anxiety, especially about leaving the protective environment of the hospital and the vigilance and availability of ward staff.

This stage of the BMT process places different demands on the BMT child and family for although the critical event is over the recovery is far from complete. Medication, weekly clinic visits, blood tests are all a continuing requirement. Children may feel tired and unwell, may object to continued restrictions and resist taking medication. Difficulties with Eating and persistent nausea and vomiting are common for a while after going home. The risk of infection is still high and the maximisation of a germ-free environment and continued isolation from children and large public groups remain necessary. Chemotherapy will have resulted in the loss of hair and the use of steroids may result in further changes in appearance which can be very distressing, particularly for the older child. Parental and sibling roles and tasks which were reorganised to accommodate the hospital admission may need to change again, although not yet back to what they used to be. Siblings may protest and voice their needs now that the family is back together. Friends may not understand, perceiving the critical event as being over. Local health and education services may not respond with the speed or degree of service that is desired. Hospital re-admissions may be necessary and this possibility should be prepared for, both practically and psychologically. In fact, family life rarely gets back to normal immediately but rather undergoes yet another reorganisation and presents a new order to adjust to.

Comments from parents two to three months after returning home highlight how difficult this time can be for some families.

-“It wasn't quite as hard as we expected while in hospital, but the adjustment to being back home was much harder than expected.”

-“Probably not prepared enough for how it hits you once you're at home - all so exhausted, lots of drugs, weekly hospital visits etc. It's not normal at all.”

-“The energy levels just went... mentally and emotionally we were drained. You don't sleep properly or eat properly in hospital; parents must be really run down at the end of the hospital stay”.

For the BMT child and siblings, these first few months after returning home can be a frustrating time. The belief that the purpose for the BMT was to improve health and quality of life may be stretched to the limit and psychological responses to the illness, treatment, separation and isolation may emerge. The nature of these responses may depend on the age of the child and their role in the BMT process and should not be confused with normal developmental changes in behaviour or concerns about issues unrelated to BMT. Younger children may behave uncharacteristically, seeking attention and constant reassurance or reverting to younger behaviours. Older children may experience and display changes of mood or become temperamentally difficult at times. Problems may develop with schoolwork or with friendships. These reactions are likely to be normal, though perhaps alarming for child and parent, and will require patience and the opportunity to discuss concerns both for the future and from the past.

Behavioural or emotional reactions four to twelve months after BMT may reflect delayed responses to the hospital period and illness in general but may too reflect concern about reaching significant milestones that clearly mark progress but can also raise fears and anxieties such as, removing a central line, stopping medications, returning to school or changing medical teams. Trusting in being cured, adjusting to a new confidence of 'wellness' from a fear of 'illness' can, for some, be a wobbly bridge to cross.

In general, it takes most families six months to a year after BMT to fully recover and adapt to the enormity of what they have been through. Awareness that recovery includes a psychological process as well as a physical one and that the ups and downs are an expected and commonly experienced part of the process may minimise disappointment and difficulties. Getting 'back to normal' can take time, but that is not abnormal.

Practical points to consider

- On returning home, do not expect too much of or from yourself, rest as much as possible and try to carve out some individual time for each child, your partner and yourself as well as family time.
- Prepare the BMT child and siblings for the certainties as well as the possibility for uncertainties that may follow the immediate discharge from hospital.
- Prepare the BMT child (and yourself) for the fact that he/she will probably receive less one-to-one attention from you and gently remind him/her of the needs of any brothers or sisters in the family.
- Do not be alarmed by swings in mood, poor concentration, poor sleep patterns or the development of inexplicable fears, in yourself or your children. Such responses are not uncommon and are usually short-lived. Do however talk these through with someone from the BMT team who can reassure you and advise you further.
- Well-meaning friends often continue to exaggerate attention on the BMT child and sibling donor (where there is one). Try to encourage an even distribution of attention: research evidence shows that, of all children, it is the non- donor sibling who is particularly vulnerable.
- Ensure that friends and family who have been supporting and helping you know that coming home does not necessarily mean that everything is better, they should not expect you to get your life back to normal immediately. Be clear about the help and support that you now need.
- Prepare the BMT child for going back to school by encouraging contact with friends (one as this is permitted). Home tuition should also be arranged for the months before the child returns to school, and schools should be made aware of what BMT involves and how your child has responded.
- Each family is different: you may or may not experience any problems post-transplant. Be prepared for them but do not expect them.

FERTILITY AND CRYO-PRESERVATION OF OVARIAN AND TESTICULAR TISSUE

The effect of the drugs used in transplant on future fertility often greatly concerns families. This article, by Dr Alison Leiper and Rebekah Lwin of Great Ormond Street Hospital looks at recent developments.

Fertility is affected in children who have undergone bone marrow transplantation using Busulphan and Cyclophosphamide as conditioning chemotherapy prior to the bone marrow infusion (if total body irradiation is used during the conditioning regimen then puberty may also be affected). The combination of these drugs acts on the ovaries in girls and testes in boys resulting in compromised fertility for almost all children, although there have been instances of spontaneous recovery of fertility some years after BMT. There is evidence that the child's age and gender and the dose of chemotherapy may all influence the likelihood of permanent infertility. Of all the possible long term effects of bone marrow transplant the probability of infertility often raises the greatest concern for parents and children.

What can be done?

At present, little can be done with any certainty of success. If the child is male and has already progressed through puberty (adolescence), then a sperm sample can be collected by masturbation and stored in the frozen state (cryo-preserved) until it is required in adulthood.

Another approach is to collect the sperm, if they are present, from the urine of a child who is near to puberty, and store these in the same way.

In the young pre-pubertal boy sperm are not present and semen cannot be collected. Other ways of preserving male fertility in this age group, are being sought. For females of any age the situation is not simple. Although eggs (oocytes) taken directly from the ovary prior to transplant can be cryo-preserved, there is a very high risk of genetic damage during the thawing procedure, which would lead to abnormality in the offspring. This, therefore, is not an option for preservation of female fertility. Currently the only feasible option is either adoption or donation of fresh oocytes from another healthy woman, at the time pregnancy is desired by the patient. This has led scientists to look for other ways of maintaining female fertility.

It is possible to obtain a wedge of ovarian or testicular tissue, containing immature eggs or sperm, by an operation under general anaesthetic, prior to bone marrow transplantation. This tissue can be successfully cryo-preserved and may eventually be the method of choice for preserving fertility. Much research is directed at trying to develop the immature eggs and sperm into mature 'gametes' capable of initiating a pregnancy. Attempts are also being made at putting sperm back into the patient's testes after BMT. However, at the present time this is only experimental and no results have been achieved in humans. Research is mainly carried out on adults who are able to give consent for this operation themselves, and where the hospital has sought permission of its Ethical Committee.

Options for the pre-pubertal child

The options for pre-pubertal children are limited but are currently under discussion nationally by paediatric oncologists (children's cancer specialists) and bone marrow transplant specialists, who work within United Kingdom Children's Cancer Study Group centres. These specialists are working towards the cryo-preservation of testicular and ovarian tissue (described above) within an ethical, acceptable, safe and legal framework, and in close discussion with the Human Fertilisation and Embryology Authority (HFEA). The HFEA govern the use of mature human oocytes and sperm (gametes) but as yet have no legislation for the use of immature gametes.

Within these discussions, the safety of the child is paramount, and following recognition that children's rights need to be respected, under the Children Act 1989, a case has been put forward that the child's fully informed consent is required. This of course is not possible with a very young child and here difficulties arise.

In the older child who is pre-pubertal, it is possible to ensure that the child has understood the information provided, by careful counselling and feedback, and in this setting it may be possible to store tissue. Experimentation is not allowed on the tissue unless Ethical Committee approval has been gained. Storage of the tissue has to take place at recognised HFEA approved centres. However, there are still many issues to be resolved such as the ownership of the tissue (e.g. does it belong to the child, the child's family the hospital?), and what happens to the tissue if the child were to die.

Great care should be taken when discussing these issues with children; that they do not confuse fertility with sexual ability or sexual identity and to offer reassurance that even though they may be infertile, they will still be able to lead an active sexual life in adulthood. Similar consideration and reassurance should also be given to boys who attempt to produce a sample of sperm themselves for storage but, for whatever reason, are unable to do so.

RISKS TO THE CHILD OF CRYO-PRESERVATION OF TISSUE

Operative risks

- The operative risks of haemorrhage, infection and general anaesthetic are greater in the female than in the male, as an abdominal operation is required.
- In both sexes the operation to remove a wedge of tissue takes place pre-BMT. This procedure exposes the child to increased risk from infection and bleeding.
- Loss of a testicle can occur through haemorrhage which may compromise a child's pubertal development.

Potential risks to the offspring

- The length of storage may be very long e.g. 20 years and it is not fully known how this length of storage will affect the immature sperm or eggs and hence the offspring.
- BMT in females is associated with pre-maturity, low birth weight and a higher perinatal mortality rate in their offspring than in the normal population.

The gene causing the immunodeficiency may be passed on to offspring who could then be carriers of the condition, or have the condition themselves in the rare cases of dominant inheritance.

Conclusions

- Although cryo-preservation of ovarian and testicular tissue prior to BMT is technically feasible and possible, research for development of immature eggs and sperms into mature gametes capable of producing pregnancy has not yet led to success in humans.
- The approach to older pubertal children is different from that of the younger child, because the ethical requirements are that the child should be fully informed and the information understood, before the parents can give consent. This is particularly pertinent when there is no guarantee of preservation of fertility, and the risks of operation may therefore outweigh the benefits.
- The different approach required for children is not always appreciated at centres dealing with adults, because of issues concerning informed and Ethical Committee Approval, where more thought needs to be given to the child's consent and Ethical Committee approval.
- The Human Fertilisation and Embryology Authority may eventually bring in legislation to govern this issue.

The increasing success of BMT has meant that it is only recently that children with severe immunodeficiencies can confidently think in terms of long-term survival and the opportunity for starting their own families. As a result, very little is known about children's attitudes towards infertility and their psychological responses to these new

techniques being offered. We need more information about the experiences of children, their parents and subsequent partners in order to understand better and inform more fully.



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