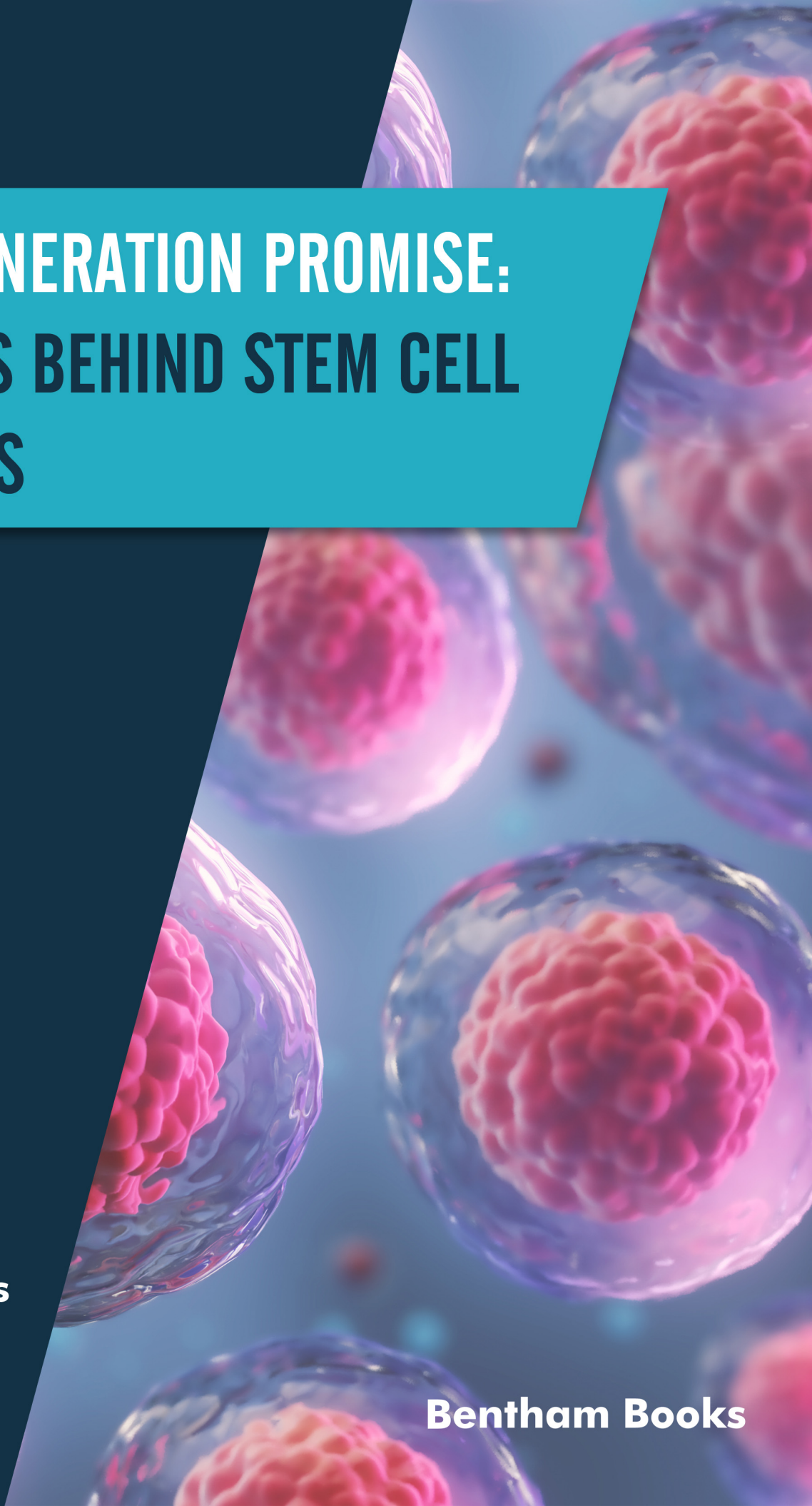
THE REGENERATION PROMISE: THE FACTS BEHIND STEM CELL THERAPIES



Peter Hollands

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Medicine Demystified

(Volume 1)

The Regeneration Promise: The Facts behind Stem Cell Therapies

Authored By

Professor Peter Hollands

Freelance Consultant Clinical Scientist
Huntingdon, Cambs PE261LB
UK

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Author: Peter Hollands

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PREFACE

The aim of this book is to bring a clear understanding and appreciation of stem cell technology and the related subject of regenerative medicine to everyone and especially to those people considering paying for stem cell therapy or stem cell related services. It avoids complex scientific terminology (or it is clearly and simply defined where needed) and develops ideas in a coherent and understandable fashion for the general reader.

The subject of stem cell technology and the related possible regenerative medicine procedures is an area of science and medicine where there is much confusion, often supported by unproven claims. There are currently many clinics offering stem cell 'treatments' which are driven by profit with no concern for the safety or well-being of the patient. There are untested and unproven stem cell based 'treatments' being offered to vulnerable patients around the globe and these are often sold at a very high price. If these 'treatments' were offered free of charge, it would still be scandalous behaviour by those offering such treatments because the 'treatments' are untested and unproven and could even pose a health risk to vulnerable, often terminally or acutely ill recipient patients.

The general public, who are the people most likely to consider, or to be offered stem cell-based therapies, in most instances often have little or no understanding of stem cell technology and put their trust in 'clinic' salesmen.

This is not the fault of the patients, it is the fault of those people who wish to draw such patients into a web of deceit.

The salesmen who represent the clinics often have no knowledge or formal training in stem cell technology at all and are all driven by profit. The result of this is that vulnerable patients, who may be suffering from life threatening or life changing diseases, are drawn into costly stem cell procedures which are at best unproven and could sometimes even be damaging rather than beneficial to their health. This must stop. This book will give everyone the knowledge to assess and reject such 'treatments' if they are inappropriate. Patients must be prepared to walk away if they have any doubts about the safety and efficacy of any proposed treatment and if a treatment does commence, it must always be under informed consent.

It is not just the general public and potential patients who need stem cell information. Many practising physicians have had little or no stem cell training in medical school, most journalists have no knowledge at all in the subject and politicians make life changing decisions on the use and availability of stem cell technology often based on a very poor level of understanding. The book will also be a useful resource to students both in school and University who want to begin their understanding of stem cell technology and become the stem cell pioneers of the future. Thorough training of our future physicians, scientists and businessmen in stem cell concepts will help resolve the problems we currently have in the clinical application of stem cell technology. The problem which we see today in stem cell technology, and the related regenerative medicine, is considerably magnified by the patient's vulnerability, confusion, fear and blind trust in an atmosphere where the unwary can lose not only lots of money but also potentially their health.

The Regeneration Promise offers truly new and thorough insight into stem cell technology and it is written in a style that anyone can easily understand. There is no complex terminology (except where absolutely needed and if the terminology is used then it is carefully explained) and the stem cell concepts are described in a simple and accessible style that can be enjoyed

and understood by all readers. The book is aimed at the general public, potential patients, physicians, students, journalists and anyone with a general interest in stem cell technology. No specialist knowledge is needed, and most importantly the information the book contains is evidence based and has no bias or hidden agenda. The Regeneration Promise is therefore a reliable and trusted point of reference for anyone either interested in stem cells or considering treatment using stem cells.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Peter Hollands
Freelance Consultant Clinical Scientist
Cambridge, UK
E-mail: peterh63@hotmail.com

DEDICATION

This book is dedicated to my partner Louise Barrett for her love, dedication and support. I must also thank my cardiac surgeon Mr. Ian Wilson and everyone at Liverpool Heart and Chest Hospital without whom none of this would be possible!

CHAPTER 1

A Bit of History

(An overview of the historical development of stem cell technology from 1956 to the present day)

A small body of determined spirits fired by an unquenchable faith in their mission can alter the course of history.
Mahatma Gandhi

Summary: This introductory chapter provides a general overview of the history of the development of the understanding of stem cell technology and the importance of stem cells to us all in everyday life. It provides important information on the basic science behind stem cell technology and it is an important foundation for readers to enjoy and understand the rest of the book.

INTERESTING TIMES

The year 1956 was interesting in many ways. Post-war recovery was progressing very well and new technology was being developed and brought into the home and the work place to make everyday lives easier and more productive. In the UK, luxuries such as the washing machine and vacuum cleaner were revolutionising the domestic role of women and optimism was high with the ending of rationing and a general post-war euphoria. In the Middle East, however, the 'Suez Crisis' brought great tension with Britain and France being drawn into military conflict in the area and Castro started a revolution in Cuba. Meanwhile, the first transatlantic telephone cable became operational while a young man called Elvis Presley was singing about his 'Blue Suede Shoes'. It was, therefore, a year of some stress (not least dirty blue suede shoes), but at the same time, this was balanced by a 'feel good' factor perhaps enhanced by the newly discovered psychedelic drugs such as LSD and derivatives which would go on to dominate 'flower power' in the 1960's. 1956 was also very important in the development of the understanding and clinical use of stem cells. Before we go any further with these ideas, it is necessary to properly understand what stem cells are and why they are important to us.

Peter Hollands

STEM CELLS ARE EVERYWHERE!

Stem cells are present in every human being, mammal and some reptiles and no doubt will eventually be found in all species in some shape or form. Stem cell science is in its' infancy and much more research is needed to come even close to an understanding of the importance and potential of stem cells. We can, however, be very certain that stem cells are essential for our normal development, normal health and possibly our ageing and eventual death. Stem cells may have been around since the first development of life on planet Earth (probably around 4.1 billion years ago) and no doubt exist in various types of life forms on other planets that are yet to be discovered (stem cells but not as we know it!).

Even in the early 21st century, we still have a lot to learn about stem cell biology and how we can manipulate stem cells to our benefit for our general health, treatment of disease and treatment of accidents such as spinal damage or burns. The unique properties of stem cells enable them to repair and regenerate tissue in our bodies for the whole of our lifespan which first develop in the early embryo at the very beginning of life. When stem cells go wrong then they can become the basis of very serious diseases such as leukaemia and cancer and understanding the nature of these 'tumour forming' stem cells will lead to a better understanding of how tumours arise and how they may be prevented or treated.

Bone Marrow Stem Cells

The most studied human stem cells to date are found in the bone marrow. Bone marrow is found inside the large bones of our skeleton, such as the thigh bone and the pelvis (hip bone). Bone marrow stem cells were the first stem cells to be discovered following many years of research on mouse bone marrow. These bone marrow stem cells in humans are capable of producing 200 billion red cells (these carry oxygen into the body and carbon dioxide out of the body), 10 billion white cells (these fight infection) and 400 billion platelets (these help to produce clots when needed) ***per day***. The bone marrow stem cells are therefore known as 'blood forming' stem cells and without them blood, and therefore human life, would not exist in its present form. This astonishing feat by bone marrow stem cells means that just over 2000 red cells, just over 1000 white cells and just over 4000 platelets are produced ***every second*** in every one of us! This is biology at its' most efficient and elegant state and we still have lots to learn about the process of forming blood, which is a remarkable process starting in the very early human embryo and carrying on until death.

The figures given above on blood cell production by bone marrow stem cells illustrate the importance of stem cells in our normal healthy lives and the enormous potential for problems when stem cells go wrong. The stem cells in the

bone marrow are truly amazing but no less so than, for example, stem cells in skin which repair and rejuvenate our skin on a daily basis and stem cells in the whole of the gastrointestinal tract (mouth to anus) which repair and maintain the cells of this vital organ. Human life would be impossible without stem cells and when stem cells either stop working or become diseased then the consequences can be severe and sometimes even deadly.

Back Again to 1956

Getting back to 1956, the significant thing which happened this year in stem cell technology was the first human bone marrow stem cell transplant in the world. Dr E. Donnal 'Don' Thomas in the USA and his team were the pioneers and the patient was an identical twin who received bone marrow from her identical sibling. Identical twins have identical genetics, which means that tissue or cells can be transplanted from one twin to the other twin without any worry of rejection of the donated tissue or cells. The recipient patient twin would have been treated with chemotherapy (drugs which destroy cancer) and radiotherapy (X rays which destroy cancer) prior to the transplant. The donor twin would have undergone a bone marrow harvest under general anaesthetic to obtain the bone marrow stem cells for transplantation. Unlike a tissue transplant, such as a kidney transplant or heart transplant, bone marrow stem cells are transplanted to the recipient patient using the intravenous route (directly into a vein). This highlights an amazing feature of bone marrow stem cells: They can be injected into a vein and they find their way to the bone marrow where they 'set-up home' and begin making blood cells. This 'homing' of stem cells is a very useful property and is often utilised in stem cell transplants to other tissue where tissue specific stem cells can 'home' to the area of damage or disease and begin their repair process.

In 1990, Don Thomas and his colleague Joseph E. Murray were awarded the Nobel prize for their pioneering work in bone marrow stem cell transplantation. Better late than never!

Tissue Typing or 'Tissue Matching'

These early bone marrow transplants were soon followed by a clear understanding in 1968 of the importance of 'matching' donor and recipient or this matching is also called tissue typing or Human Leucocyte Antigen (HLA) typing. Donors and recipients of bone marrow can be 'matched' to avoid or minimise 'rejection' or what is technically known as graft *versus* host disease (GvHD). This work was carried out by Dr. Jean Dausset and his colleagues Dr George Snell and Dr Baruj Benacerraf. These three scientists shared the Nobel prize for their work on tissue typing in transplantation in 1980. Once again better late than never!

CHAPTER 2

Blood and Toil

(Bone marrow transplantation and other applications of bone marrow stem cells)

I have nothing to offer but blood, toil, sweat and tears.
Winston Churchill

Summary: In this chapter, you will learn about the amazing work done with bone marrow transplants to treat leukaemia and blood disorders. This is not an easy process for either the patient or the healthcare professional, but it is a tried and tested treatment for otherwise deadly diseases. There is also a discussion about the nature and importance of clinical trials using bone marrow stem cells to treat a whole range of disease, which is followed by a note of caution to anyone considering such treatment provided by some private clinics outside of registered clinical trials and in areas of the World where regulation of such technology is either weak or non-existent.

'BLOOD FORMING' STEM CELLS

Prior to 1956, the diagnosis of leukaemia and related blood disorders meant that the only outlook was a long, slow, painful death. Once bone marrow transplantation became routine in the 1970's, then effective treatment was a reality. Nevertheless, the treatment process was still technically challenging and not a simple procedure either for the bone marrow donor or the recipient patient.

Before I go any further with this important discussion about bone marrow stem cells, I would like to make one important point very clearly:

'Blood forming' stem cells (whether obtained from bone marrow or *via* peripheral blood or 'blood forming' stem cells from cord blood) are the **only** stem cells in routine clinical use to date and bone marrow stem cells (which includes peripheral blood stem cells) are considered the gold standard for the treatment of blood diseases.

This is extremely important because it clearly emphasises the current and future clinical importance of 'blood forming' stem cells from bone marrow. It also

strongly refutes any unproven, untested and unsafe 'treatments' offered by 'clinics' around the World.

There are many Centres of Excellence around the World carrying out 'blood forming' stem cell transplants. Any patient who has to undergo 'blood forming' stem cell transplantation to treat a blood disorder such as leukaemia can be assured that the process is as safe as it can be and that it is supported by considerable amounts of expertise and medical evidence. This medical evidence, usually obtained from papers published in respected medical journals, is known as the evidence base. Stem cell 'clinics' offering untested and unproven 'treatments' almost always have no evidence base or an evidence base, which is either controversial or simply untrue.

The fact that 'blood forming' stem cells are ***only*** tried and tested in the treatment of blood disorders is extremely important, especially in the light of claims by some companies that bone marrow and/or cord blood stem cells can treat a wide range of diseases unrelated to blood diseases. These claims, without exception, are **all** false or at best based on poor, contradictory, weak or non-existent evidence. When examined closely, it is clear that bone marrow based 'therapies' of this sort are based on hype and untested ideas, and at best can only be supported by incomplete or ongoing clinical trials, which is the way in which such concepts are tested and validated for routine use. The fact that a clinical trial is underway ***does not*** mean that the safety and efficacy of the subject of the clinical trial are in any way proven. It is only proven if and when the clinical trial is complete and the data show that the subject or treatment being tested proved useful and safe. Even at that point, there could then be many years before the technology in any clinical trial comes into safe routine use. The basic point is that if something is in clinical trial, then it is unproven until it is proven!

There are many workers carrying out research into bone marrow stem cells and creating some interesting and possibly useful information. However, these ideas are *research* and nowhere near clinical application. Such ideas must not be referred to as 'evidence' for clinical use especially by unregulated 'for profit' clinics. They are all interesting examples of basic laboratory research, which may lead to clinical applications in the future. Jumping from basic laboratory research to clinical applications, without clear data on safety and efficacy from *completed* clinical trials which showed a clear benefit, is an extremely dangerous process. It is, however, a very tempting proposition for people who want to make money from vulnerable patients using untested technology.

The only source of 'blood forming' stem cells which even comes close to bone marrow in terms of clinical importance is cord blood. This technology will be

explained in detail in Chapter 3. This is therefore, the first big surprise in the Regeneration Promise, which may give the impression that we are routinely using stem cells left, right and centre to treat a whole range of diseases: ***We are not***.

The truth is that bone marrow stem cells (remember these are 'blood forming' stem cells) are routinely used to treat leukaemia and blood disorders, which amount to about 80 different blood diseases when you take into account the various types of leukaemia and genetic disorders which affect the blood system. This makes bone marrow stem cells, *without any doubt*, the most important stem cells in routine clinical use and the basis of all of the subsequent ideas on regenerative medicine and stem cell technology.

Bone Marrow Transplantation

In order to put the clinical use of bone marrow transplantation into perspective and to understand that even bone marrow stem cells are not a perfect or easy option, it is useful to better understand the transplantation process.

The first step in a bone marrow transplant is the initial diagnosis of disease in the recipient patient. In terms of leukaemia this would involve initial blood tests and then taking a small amount of bone marrow, usually from the breast bone under a local anaesthetic, and examining this under a microscope to work out which type of leukaemia or other blood disorder is present. Other genetic blood diseases, such as sickle cell anaemia and thalassaemia can be diagnosed using standard blood tests.

Once we have the diagnosis then the second step is to find a suitable matched bone marrow stem cell donor. This can be a difficult process for some patients. The first stop in this search for a bone marrow donor is usually family members, but surprisingly, this is often unsuccessful unless identical twins are involved, which, as mentioned earlier, are a perfect match for each other. More recently, however, family members have started to be used as donors for 'haploidentical' bone marrow transplantation.

The problem with finding a bone marrow donor is that the donor and recipient must ideally be a 99-100% tissue match. Any bone marrow where the tissue match is less than 99-100% is likely to cause major, potentially fatal GvHD (rejection) complications in the recipient patient. Few transplant physicians will take the risk of using poorly tissue matched donor bone marrow as the outcome for the recipient patients has been shown to be very poor.

CHAPTER 3

A Bouncing Baby!

(The introduction of umbilical cord blood stem cell transplantation and CP/autism research)

A baby is like the beginning of all things – wonder, hope, a dream of possibilities.
Eda J. Le Shan

Summary: This chapter provides an introduction to cord blood stem cells and how they can be used in the treatment of leukaemia and blood disorders. The pros and cons of using cord blood stem cells for transplantation are also discussed. It also explores the ground-breaking clinical trials on the use of cord blood to treat cerebral palsy and autism.

CORD BLOOD STEM CELLS

In chapter 2, it was mentioned that cord blood is a useful source of 'blood forming' stem cells which can supplement and sometimes even replace the tried and tested bone marrow stem cells. In this Chapter, I will describe the use of cord blood stem cells, which have now been used to treat over 80 blood disorders, including leukaemia and related blood diseases, since the first transplant in 1988.

When a baby is born anywhere in the World, there is quite rightly great joy for the new life it brings. New parents, grandparents, uncles and aunts all wish the new baby health, wealth and happiness. Foremost of all of those is health and we all wish that all children could remain in good health. Sadly, this is not the case and some children will inevitably go on to develop serious life-threatening diseases such as leukaemia and cancer. Many of these children will die simply because of the lack of a suitable bone marrow donor, as described in earlier chapters. There is a simple and effective solution for some of these children and small adults and this is umbilical cord blood stem cell transplantation.

Cord Blood Stem Cell Collection Process

When a baby is delivered, and the umbilical cord is clamped and cut, there is the blood left in the umbilical cord and placenta. This 'cord blood' contains life

giving 'blood-forming' stem cells which could potentially one day save that baby's life, the life of a member of the baby's family or even the life of an unrelated patient. The stem cells found in cord blood are stem cells which are capable of replacing diseased or damaged bone marrow. In the case of the umbilical cord blood, the 'blood forming' stem cells are present in large numbers and they are capable of forming all of the cells of the blood system.

The collection of umbilical cord blood stem cells is very simple. Once the baby has been born, and the umbilical cord has been clamped and cut, it is simply a matter of putting a needle into the umbilical cord and allowing the blood to drain into a specially designed cord blood collection bag. This process, collecting cord blood before delivery of the placenta, is shown in Fig. (**5**). Most cord blood today is collected after the delivery of the placenta. The process takes no more than 2-5 minutes. The cord blood is collected by a trained phlebotomist and it does not interfere in any way with the birthing process or different birthing practices such as water births. Research and development are underway to optimize this collection process, perhaps using automation, so that the volume and quality of cord blood collected can be maximised, which will in turn, increase the clinical utility of cord blood.

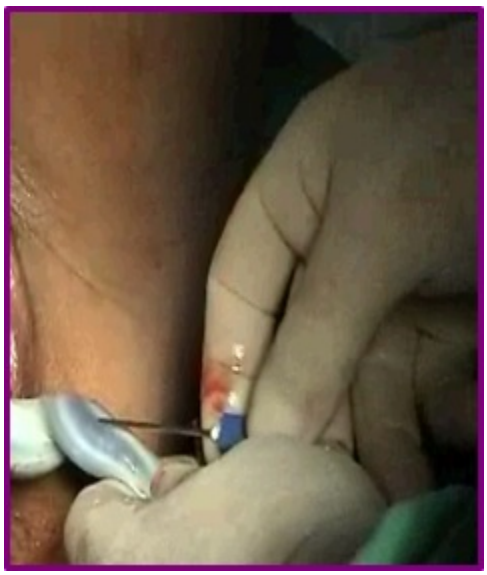

Fig. (5). The collection of umbilical cord blood before delivery of the placenta.

Cord Blood Stem Cell Storage Options

There are commercial companies around the World offering private cord blood collection and storage to pregnant women for a fee (usually between £3000-

5000). The fee covers the collection, processing and first year of storage for the cord blood stem cells and there is an additional annual storage fee (usually about £100 per year). The concept here in these private cord blood banks is that the stored cord blood can be used to treat the baby or a family member (most commonly siblings or parents) if needed. The chance of such cord blood being needed for family use is around 1:1000, so there are many privately stored cord blood stem cells which are never used.

The other option for pregnant women is to donate their cord blood to a public cord blood bank where it will be made available to anyone in need. This does not cost the pregnant mother anything and the chance of using the cord blood is much higher. Nevertheless, if the cord blood stem cells are needed in the family, then there is no guarantee that they will still be available. The subject of private *versus* public cord blood banks is discussed in detail in Chapter 4.

Following collection, the cord blood bag is then placed into a shipping container and sent to the processing laboratory using a medical courier. The cord blood collection bag does not need any special treatment, it is kept at room temperature and the stem cells it contains are stable for up to 72 hours following collection. The collection of umbilical cord blood as described has no effect whatsoever on the baby or the mother.

Cord Blood Laboratory Processing

On arrival at the laboratory, the cord blood collection bag is carefully assessed by carefully trained scientists to ensure that no damage or adverse temperature variations have occurred during transport. The collection kit is designed to provide optimum protection to cord blood during transit to the laboratory. Once accepted and shown to be safe, the cord blood is then processed. The processing is the same for public and private cord blood banks.

The processing most commonly involves the removal of excess plasma and red cells from the cord blood by using the validated technology such as the widely used Sepax system. The volume reduction achieves a concentrated (the total volume is 25mL) solution of the potentially life-giving stem cells in a bag about the same size as a credit card. The cord blood stem cells are then slowly frozen from room temperature to -180°C in a controlled rate freezing machine (such as that produced by Planer) to final storage in liquid nitrogen at -196°C. The liquid nitrogen tanks in which cord blood stem cells (and other stem cell types) are stored have 24/7 monitoring and alarm systems which alert the laboratory staff if the storage temperature goes out of range. The stem cells are completely stable at this very low temperature (biological activity is stopped and kept in suspended animation) and can be stored for many years. Samples of umbilical cord stem

CHAPTER 4

Baby Blues

(The issues surrounding public and private cord blood storage and use)

We are our choices This is a quote.
Jean-Paul Sartre

Summary: This chapter explores the subject of public and private cord blood collection and storage and tries to answer some of the frequently asked questions about these services. It provides specific advice for those people considering private cord blood banking and explains the pros, cons and practicalities of cord blood collection and storage. Private cord blood collection and storage has become an enormous business on a global scale, but it is extremely important that the clients of these private cord blood banks fully understand the exact uses and limitations of what is on offer. Ultimately private storage is a matter of personal choice and, of course, a matter of having sufficient money to pay for private cord blood storage.

CHOICES

Life is full of choices. Our partners, our home, a car, when and if to have children, the colour scheme for the lounge and even what to eat this evening. Our whole lives, and the relative success of those lives, are based on choices. Bad choices: bad life. Good choices: good life. We all understand this and we all try our very best to make good choices but inevitably, things can go wrong. This is the human condition, we cannot all be right all of the time. Even I might have made some poor choices in the past, but that is a different and scary story!

There is now another choice to add to that list and this is whether or not to collect and store cord blood from the birth of a baby to create a source of stem cells for family if needed. This is perhaps one of the most complex choices asked of parents, at a time when parents (and especially first-time parents) have quite a bit on their minds. The cord blood choice is something for which they are ill prepared, and sometimes ill informed, to make, and this can result in the permanent loss of some of the most precious cells in the world, which have the ability to save a life. Life is all about choices.

The conundrum when thinking about private cord blood collection and storage is that if a choice is made to store cord blood, it might never be needed and if a choice is made to discard cord blood, then there is no second chance unless there is a second baby.

Public and Private Cord Blood Banks

The previous chapter introduced cord blood stem cells and mentioned the existence of private and public cord blood banks. It is now important to explore this subject a little more because cord blood stem cells are present at the birth of every child and there is a clear choice on what to do with this valuable material: collect and store it for future use if needed or burn it with all the medical waste.

First of all, we need some clear definitions:

Private cord blood banks collect and store cord blood for *family use only* for an initial fee and an ongoing annual storage fee.
Public cord blood banks collect and store altruistically donated cord blood for use by anyone in need. There is no cost to the cord blood donor.

The pregnant woman and her partner are often therefore faced with several difficult choices regarding the fate of their cord blood:

Do we pay to store cord blood stem cells privately which will be kept for our family use only and pay a relatively large collection, processing and storage fee and recurrent annual storage fees to do so?
Do we donate the cord blood to a public bank for general use, which will cost us nothing and could help someone in need?
Do we simply ignore the issue altogether and allow the cord blood to be discarded along with the placenta and umbilical cord as medical waste?

The answer in part to these questions may be relatively simple if the parents have a low income and simply cannot afford private collection and storage, which costs about £2000 in the UK, about twice as much in the USA and about a quarter as much in India. These prices around the world may, of course, relate to the relative income of clients and also the income of those working in private cord blood banks (which has to be paid by the income produced from clients) in these countries. They also reflect the expensive technology, highly trained staff, complex facilities, licensing and accreditation costs and expensive high-cost consumables used to collect, process and store cord blood. These costs, of course, vary enormously from country to country.

What would be a better approach is if public health providers (for example, the NHS in the UK) or health insurance companies or companies as a perk of employment could fund the private collection, processing and storage of cord blood for *all* pregnant women. It may even be possible to add cord blood to the existing organ donation legislation in the UK, making cord blood collection automatic unless the mother opts out. This is something which politicians need to hear and make decisions. The cost of this to the health care provider would be high, but no higher than other services and the potential benefits would be enormous. The NHS does currently fund some cord blood banking in the UK but it is for public not private use and it is very restricted. This restriction is because cord blood can only be collected in certain hospitals in the UK so that many pregnant women who wish to donate cord blood cannot. There is also no infrastructure in the UK or elsewhere to enable cord blood donation by all pregnant women.

The Development of Private Cord Blood Banking

In the early days of private cord blood stem cell banking in the early 1990's the advertising used by some private cord blood banks was far from ideal in that some would suggest that private cord blood storage should be carried out by parents because it may save the life of their baby. This is wrong at many levels.

Firstly, the chance of the baby him/herself needing the cord blood and the stored cord blood stem cells being suitable for treatment is remote. Several people have tried to estimate this chance and values from 1:10,000 and 1:100,000 have been suggested. It is safe to assume that privately stored cord blood is highly unlikely to be needed by, or used by, the baby. There is also some evidence that some diseases which are seen in the baby could start during early fetal development. If this proves to be the case, and for some diseases the evidence is becoming more and more convincing, then the stem cells from that baby could simply be the source of more disease once transplanted back to the baby. The fact is that most, if not all, babies will have a better outcome in cord blood stem cell transplantation for blood disorders if the stem cells for transplant come from a matched donor rather than from the baby him/herself.

Secondly this type of marketing, where the parents are led to think that their actions could be the difference between life and death for their baby, is totally unacceptable emotional blackmail. Luckily, this type of advertising by private cord blood banks has now been outlawed by the regulatory authorities and private

cord blood banks are now, *in most countries at least*, obliged to use factual material in their marketing with no emotional blackmail.

CHAPTER 5

That's a Nice Vein

(The introduction and use of peripheral blood stem cells)

Blood is a very special juice.
Johann Wolfgang von Goethe

Summary: This chapter considers the impact which has been made by the introduction of peripheral blood stem cell transplantation into routine clinical practice for the treatment of leukaemia and other blood disorders. The process helps in the collection of 'blood-forming' stem cells from bone marrow, and peripheral blood stem cell transplantation has now become the first-line treatment for most blood disorders.

PERIPHERAL BLOOD STEM CELLS

The introduction of the use of peripheral blood (taken from blood in the veins) stem cells in 1986 into routine clinical practice for the treatment of leukaemia and blood disorders represented a quantum change in the practice of bone marrow stem cell transplantation. The basic principle here is that adult 'blood-forming' stem cells normally live in our bone marrow (mostly in the pelvis and the long bones such as those in the thigh and lower leg). In order to harvest these stem cells for transplantation, it is necessary to carry out multiple puncture sites under general anaesthetic, from the pelvis. This is a relatively painful process which also carries the normal risks associated with a general anaesthetic, along with potential problems from bleeding or infection. Nevertheless, the traditional bone marrow harvest was critical in the early development of 'blood-forming' stem cell transplantation, and this process has saved thousands of lives globally.

The technology used in peripheral blood stem cell harvesting is very different from that used in a 'traditional' bone marrow harvest. The target cells for the collection are still the same 'blood-forming' stem cells which normally sit in the bone marrow, but peripheral blood stem cell technology enables a much easier collection of these stem cells making the whole process less traumatic for the donor, less risky for the donor and more cost-effective both for the donor, recipient and healthcare provider.

Peter Hollands

The key behind this technology is the ability to make 'blood-forming' stem cells leave the bone marrow and enter the peripheral circulation. This has been achieved by using a combination of medications which reduce the 'stickiness' of 'blood-forming' stem cells and allow them to enter the general circulation from the bone marrow. Once in the general circulation, these 'blood-forming' stem cells can be collected using a process called apheresis. In straight forward terms, apheresis is a very specialised centrifuge that can separate the stem cells from the rest of the blood cells. The process of apheresis is carried out by specially trained nurses or technicians as a 'day case' in hospital.

Following 'blood-forming' stem cell mobilisation into the peripheral blood by the use of medication, the patient is attached to an apheresis machine which draws blood from the patient and the patients' blood, containing stem cells, flows into the apheresis machine. The apheresis machine then separates the stem cells from the rest of the blood cells in the patients' blood. It keeps back the stem cells in a collection bag in the apheresis machine and returns all of the other blood cells and plasma back to the patient.

The stem cells obtained from the apheresis machine can then be frozen for later use either for the patient themselves or can be donated to another person. When the stem cells are later used by the patients themselves, this is referred to as an 'auto-transplant' or 'autologous transplant'. The scenario of an autologous transplant is usually when the patient has a blood disease that needs a stem cell transplant. When the stem cells collected by the apheresis machine, the patient receives treatment for the disease (*e.g.*, chemotherapy and/or radiotherapy), and once the treatment is complete and the disease has been eradicated, the patient receives their own stem cells back in a transplant as described earlier.

When the stem cells are donated to another person, this is referred to as an 'allo-transplant' or an 'allogeneic transplant'. Allogeneic transplantation from an unrelated donor to a recipient patient still requires the tissue match between donor and recipient in the same way as the bone marrow stem cells. This is because peripheral blood stem cells are just bone marrow stem cells which have been mobilised into the peripheral circulation and have exactly the same biology as they do when they are collected from bone marrow directly.

This collection of peripheral blood stem cells from unrelated donors has resulted in a revolution in stem cell donation because of the relative ease in which a donor (or indeed the transplant patient themselves in the case of an autologous transplant) can make their donation. Previously, a donor would have to undergo a bone marrow harvest under general anaesthesia, but now they can donate their

stem cells by a relatively easy and non-invasive process, which makes stem cell donation more attractive to altruistic donors.

Organisations such as Anthony Nolan in the UK now collect stem cells from their donors using apheresis, and they even carry out the initial tissue typing by a simple 'cheek swab', making the process quick and easy. The potential donor is sent to a specially designed swab, which is used by the donor to collect a few cheek cells from inside the side of the mouth. The DNA in these cells is then examined in the laboratory, and from this, the basic tissue type of the donor can be assessed, and this is sufficient to match the donor to a potential recipient. If the transplant is to proceed further, blood tests from the donor are needed, but the initial 'cheek swab' is a great way to get potential donors onto the database and has made the initial donor registration process much more attractive to prospective donors. This means that more potential donors are now on the database, which in turn means that more lives can be saved.

Potential Problems

As with all things in life, nothing is perfect (not even me), and the peripheral blood stem cell process is no exception. The main problem which can arise is that the medication fails to release enough stem cells from the bone marrow, or it might even fail to release any stem cells at all. This can be a particular problem when older patients (40 years plus) try to undergo peripheral blood stem cell mobilisation. In general terms, the older the patient, the less likely successful stem cell mobilisation can be achieved. This means that not enough stem cells are collected for treatment, which of course, can have a big impact on the patient, especially if it is an auto-transplantation (using the patient's own bone marrow) with no back-up source of stem cells. The apheresis technology is also relatively expensive, and the people who operate it need specialised training, and finally, children do not tolerate apheresis very well. In general terms, apheresis is not used when a child needs a stem cell transplant using his or her own cells. It is, of course, possible for an adult to donate peripheral blood stem cells for the treatment of a child.

Despite these potential problems, peripheral blood stem cells are by far the most common treatment route for leukaemia and blood disorders and are considered by most practitioners as the 'gold standard'. This means that you can feel safe and re-assured if you are a patient undergoing peripheral blood stem cell transplantation in a recognised treatment centre.

CHAPTER 6

The Vatican and More

(Concepts and controversies surrounding human embryonic stem cells)

And many false prophets shall rise, and shall deceive many.
Peter J. Tanous

Summary: This chapter examines the debates, and sometimes the hope *versus* hype, which surrounds embryonic stem cells and their potential use in clinical transplantation. The use of human embryos in stem cell technology creates many strong opinions from a surprisingly wide range of people. This chapter explores the pros and cons of embryonic stem cells and gives an overview of the possible future for embryonic stem cells.

A COMPLEX DEBATE

It is sometimes very surprising who becomes involved in debates about stem cell transplantation and regenerative medicine. The most likely people to be interested are scientists, clinicians, the media, regulatory authorities, and, of course, the many companies who produce the equipment and chemicals needed for the stem cell manipulation and transplantation process.

Occasionally, potential patients, actual patients or celebrities have become involved in the debate. For example, Christopher Reeve (of Superman fame) became a great advocate for embryonic stem cell technology following his tragic spinal injury. Unfortunately, human embryonic stem cells are yet to be used to treat spinal damage, and they were never made available (at least they were never reported as being made available) to Christopher before his unfortunate death.

There are also private clinics worldwide that provide stem cell therapy and who are very vociferous, if not often misinformed, misled, or simply led by profit, about their chosen type of stem cells. Such companies have a clear financial interest to promote the use of stem cell technology, which may persuade them that providing proof of safety and efficacy of their stem cell products is a hindrance to their progress.

The clinicians, scientists and others working in stem cell technology usually get together in international conferences (which in the post-Covid19 future will hopefully happen virtually) to discuss new ideas and confirm old ideas. These are often the most constructive discussions which focus on stem cell facts and not hype and myth. The development of embryonic stem cells, derived from human embryos as a potential source of stem cells for clinical use, has brought many more people into the debate, including religious leaders of all faiths, medical ethicists, medical lawyers and of course, the media and journalists also want to join the party!

Human Embryonic Stem Cell Production

In order to properly understand why there is so much interest from so many different people about human embryonic stem cells, it is necessary to understand the basics of their creation and the potential of their use.

Embryonic stem cells are extracted from a human embryo five days following fertilisation of the human egg with human sperm. This fertilisation process must be carried out in a laboratory and is, therefore, always part of an *in vitro* fertilisation (IVF) procedure. The embryo at this five-day stage after fertilisation is called a blastocyst, and it is a hollow ball of cells (consisting of about 120 cells in total), and it is about 0.1mm in diameter. Such an embryo can just be seen by the naked eye, but under a low power microscope, the beauty of the blastocyst can be clearly seen. The walls of the ball which forms a blastocyst are uniform apart from one area where the cells are thicker, this is called the inner cell mass. The inner cell mass is the area of the embryo, which will eventually develop into the baby, and the thinner, more uniform area (the trophoblast) of the blastocyst will develop into the placenta and membranes of the pregnancy, such as the amniotic membrane. In order to obtain human embryonic stem cells, it is necessary to dissect the inner cell mass from the rest of the human embryo and grow the dissected cells in the laboratory for several more days. It is this process, which results in the destruction of a human embryo and the creation of human embryonic stem cells, which has sparked the medical, financial, legal and religious interest of so many people and created worries in others.

The Human Embryo

The key thing to remember here is that a human embryo is a small collection of cells that is the basis of human life. Some theologians (most notably past and possibly present Popes) and ethicists object to the deliberate destruction of human embryos even when the purpose of the destruction is to obtain human embryonic stem cells to treat other human beings in need. They see it as the death of human

life (even killing or murder in some minds) to treat another human life; it is viewed as unacceptable to them.

It is also very important to ask where the human embryos are obtained for the creation of human embryonic stem cells. The answer is that all embryos come from 'unwanted' frozen human embryos in IVF clinics around the world. These are most usually from successful IVF treatment cycles where the parents have achieved the family they desire, and the frozen embryos remaining at the IVF clinic are no longer needed for fertility treatment. The parents have the option in most countries to either simply destroy the frozen embryos, donate them to another couple or donate them to research where the primary purpose will be to create human embryonic stem cells. This situation is unique in embryonic stem cell technology, where the 'donor' is a human embryo, and the embryo cannot give informed consent for the process. Informed consent is obtained from the parents of the embryos prior to any manipulations to create embryonic stem cells. This represents the best option available to ensure consent in the embryonic stem cell process.

All of the other stem cell donors discussed in this book are either from adult human donors who have given informed consent themselves, or the stem cells are obtained from the 'waste products' of childbirth, from fat liposuction or from teeth, which would otherwise be discarded. The consent process in all of these is very clear, and in these cases, the patients from which the 'waste products' are obtained have given their informed consent to further use their tissue.

It is clearly impossible for a frozen human embryo to give its' consent for anything, and for many people, who view the human embryo as an individual human, this is a serious cause for concern. Some people even consider the dissection and destruction of a human embryo to obtain human embryonic stem cells as a form of 'murder' in that the potential for human life has been taken away. This is a complex debate that is far from concluded even today and perhaps will never be resolved to the satisfaction of everyone involved.

The stem cells obtained from a human embryo are different from other types of stem cells in that they have the potential to form any type of tissue in the body and could therefore be used, in theory, to treat an almost never-ending list of diseases. This fires up the imagination, especially that of the media, that embryonic stem cells could be the panacea for disease. Sadly, this is not true, and it is not even close to being true for the reasons which are discussed below.

CHAPTER 7

No One Likes the Dentist

(Ideas behind dental pulp stem cells)

I always wanted to be a dentist from the time I was in high school, and I was accepted to dental school in the spring of 1972. I was planning to go, but after the Olympics, there were other opportunities.
Mark Spitz

Summary: This chapter summarises the amazing progress which has been made from the discovery that there are 'tissue forming' stem cells inside teeth which can be 'extracted' and potentially used as the basis of future therapies. The process of dental stem cell collection and storage is described along with an overview of the potential applications of dental pulp stem cells.

OFF TO SEE THE DENTIST

A trip to see the dentist can mean many things. Fear, apprehension, relief (if you have toothache) and sometimes elation when the diagnosis of 'all clear' is given for another six months. Whatever your emotions, there is a relatively new concept in dentistry which has caught the imagination of stem cell scientists and increasingly some dentists. This excitement comes from the discovery of the presence of 'tissue forming' stem cells *inside* teeth which can be collected, processed, stored and potentially used in the treatment of a range of diseases.

Milk and Adult Teeth

Everyone is familiar with 'milk teeth', which are the first teeth a child develops, and these 'milk teeth' naturally fall out around age 5-6 years and are then replaced by permanent 'adult teeth'. Researchers have shown that both 'milk teeth' and 'adult teeth' contain 'tissue forming' stem cells with the possible potential to be useful in regenerative medicine and even possibly in dentistry.

Milk Teeth Collection

When a child naturally loses a 'milk tooth', it is possible to collect the tooth, place

it into a transport medium such as saline containing antibiotics, or even milk, and send it to a laboratory to be processed and frozen. On arrival at the laboratory, the tooth is split open to expose the internal tissue (called dental pulp) which contains the stem cells, and the whole opened tooth is then frozen using liquid nitrogen in a special freezing solution which protects the stem cells.

There are, however, some practical problems with the collection, processing and storage of 'milk teeth' which have possibly contributed to the general lack of uptake of such a service:

> Firstly, the tooth fairy is furious and is considering legal action.
> Secondly, a single 'milk tooth' contains very few stem cells, so as a practical proposition to provide stem cells in the numbers needed to be clinically useful, it would need several, if not all, of a child's 'milk teeth' to be collected and stored.
> Thirdly, most regulatory authorities require the donor of stem cells, in this case, a child, to undergo infectious disease screening at the time of donation. In practical terms, this means that the child would have to undergo a blood test and be screened for HIV, hepatitis and syphilis. This could be traumatic for some children and parents considering 'milk tooth' collections and storage.

In summary, 'milk teeth' stem cell collection and storage are not to be recommended at present because the cost and invasive testing of the child are not balanced by the benefits. 'Milk teeth' stem cells have no current clinical use, although they may be useful in future clinical trials, especially in the creation of bone in patients where the bone loss in the jaw is causing dental problems. It is likely that if such applications become routine, then the stem cells from many 'milk teeth' would either have to be pooled together to treat one patient or the stem cells would have to be expanded in the laboratory.

Stem Cells from Adult Teeth

The second area of interest in dental pulp stem cell technology involves those 'tissue forming' stem cells which have been shown to be present inside adult teeth. The proposal here is that when an adult has a *healthy* tooth extracted, either for impacted wisdom teeth or for orthodontic reasons (overcrowding), then the tooth can be sent for adult stem cell processing and storage following the same process described above for 'milk teeth'. The adult donor has to undergo infectious disease screening as described above but this is of course less invasive than doing this on a child and the blood could easily be taken at the time of extraction of the tooth. Adult teeth are of course physically larger than 'milk teeth', and as such, each adult tooth contains more stem cells and the potential of these stem cells to be useful in the future is slightly increased. There is still,

however, considerable uncertainty as to whether or not adult teeth stem cells will have any useful application in the future. Therefore, there is no evidence to support collecting and storing adult teeth at present.

The relatively simple process of collecting and storing 'milk' and 'adult' teeth has resulted in the development of companies which specialise in tooth collection and storage, such as Bioeden in the UK. Tooth collection and storage have also now been added to the services provided by most private umbilical cord blood banks. This made the relatively low demand tooth collection and storage service a viable business proposition to existing cord blood banks as a service 'add on' and some companies even predicted significant profits from the service; these profits have yet to be materialised.

Are There Enough Stem Cells?

The main problem with both baby teeth and adult teeth in terms of stem cell therapy is that neither source contains very many stem cells. This means that to use these cells in current treatment or clinical trial procedures as 'tissue forming' stem cells would require either some sort of cell expansion in the laboratory prior to use or to pool the stem cells from many teeth. This would increase the number of stem cells available for treatment. The expansion would, however, be using chemicals and/or bioreactors to increase the cell numbers and this would make the final product a 'pharmaceutical'. This puts the expanded dental stem cell product into a category which requires a very high level of regulation.

Pooling the stem cells from several teeth is simple enough but this would rely on a person having several teeth stored which is unlikely. This is especially unlikely for 'adult' teeth unless both wisdom teeth have been stored or several teeth have been extracted for orthodontic reasons and stored. It is theoretically possible to collect all of the 'baby' teeth but in practice this is unlikely to happen. The parents of young children will understand why!

This makes the whole process unattractive as a source of 'tissue forming' stem cells for clinical use when tissue such as fat can provide the number of stem cells needed without any expansion.

Tooth Implants

The only scenario where teeth stem cells could *possibly* be used without expansion is surprisingly enough in dentistry. This is in the area of tooth implants which are becoming a very popular way to replace lost adult teeth. The concept here (without getting into too much gory dental surgery detail) is that the dentist screws an implant into the empty tooth socket and then attaches a permanent

CHAPTER 8

Who Are You Calling Fat?

(Ideas behind adipose or fat stem cells)

The devil has put a penalty on all things we enjoy in life. Either we suffer in health, or we suffer in soul, or we get fat.
Albert Einstein

Summary: This chapter describes the progress which has been made in the identification, collection, processing, storage and clinical use of fat or adipose stem cells. The technology is developing very rapidly and the application of adipose stem cells in both routine therapy and clinical trial is increasing rapidly.

FAT: GOOD OR BAD?

We all carry fat around and, in small amounts, it is essential for normal health. Many of our organs, especially the central nervous system, need fat in order to operate properly. Some nerves, for example, are covered in a 'fatty sheath', which provides insulation for the nerve impulse in the same way that plastic insulates an electrical cable. Loss or damage to this fatty covering in nerves results in serious diseases such as multiple sclerosis.

Nevertheless, due to poor diet, lack of exercise and an easy access to high fat food in some countries, many of the population are obese (carrying too much fat around) or morbidly obese (a patient who carries so much fat that there is a clear danger of serious life-threatening illness resulting from the excess fat). Fat therefore has a bad image and fat is generally seen as a bad thing with no real benefit. However, things might be changing.

The change has been driven by the discovery that fat contains 'tissue forming' stem cells which can be harvested and potentially used to treat a wide range of disease. Plastic surgeons have in fact been using the patients' own fat in reconstructive and cosmetic surgery for decades but the discovery of adipose (fat) stem cells opens up many new potential therapeutic options.

Peter Hollands

Liposuction

The initial studies on fat stem cells focussed on the fat which is collected when a person undergoes liposuction to remove excess fat from the abdomen. This is a surgical procedure, requiring a general anaesthetic, and it carries the usual risks of

bleeding and infection associated with such invasive procedures. Most liposuction procedures are carried out in private clinics as major public health care providers

such as the NHS tend to exclude the procedure (because it is considered to be a cosmetic procedure) unless it is required as a treatment of related diseases.

When a liposuction procedure is carried out, it is possible to obtain up to 5 litres of fat weighing up to 11 pounds. In the past, this fat has been discarded as medical waste but patients now have the option to send it on for processing and storage of the 'tissue forming' stem cells found in the fat. This storage is carried out by existing private cord blood banks who were quick to add fat to their range to produce another income stream.

Processing of Fat Stem Cells Using Enzymes

These amounts of fat, obtained from liposuction, do however present quite a challenge to the processing laboratories. Firstly, it requires expensive reagents and equipment to process the fat which make the overall process quite costly. Secondly, the processing involves the use of enzymes which are chemicals and which allow the release of the stem cells from the rest of the fat cells. The use of enzymes is not in itself a problem, in fact enzymes enable good collection of stem cells, but the regulatory authorities (such as the MHRA in the UK) view the use of chemicals such as enzymes as an increased level of manipulation. This increased manipulation using enzymes means that fat stem cells attract the attention of regulatory authorities who more usually regulate pharmaceuticals. This is not a problem in itself but the increased level of regulation, when using enzymes to process fat, results in increased costs in terms of regulatory, staffing, facilities and equipment costs. This increased cost makes the collection, processing and storage of fat stem cells using enzymes not really a practical proposition, and as such, has held back some developments in fat stem cell technology.

Processing of Fat Stem Cells Using A Mechanical Approach

A recent solution to this problem has been proposed by several researchers who have discovered that fat can be processed by mechanical means to extract the stem cells. This mechanical digestion of the fat commonly uses a selection of clinical grade blades (inside a sterile, small single use box) through which the fat is

passed. This approach considerably simplifies the processing of fat and the extraction of fat stem cells. Mechanical processing of fat tissue takes away the extra regulation which enzyme treated fat stem cells attracted, which in turn reduces the cost of using fat stem cells.

This mechanical digestion technology is a major breakthrough in fat stem cell technology as it has changed the process from being complex and expensive to being relatively easy and cheap. Many physicians have, in fact, already used this mechanical digestion technology and have developed a system which can collect fat. Small amounts of fat (10-20mL) can be collected under local anaesthetic at the bedside or larger amounts in the operating theatre. The fat is then immediately processed using mechanical digestion technology and then immediately used either for cosmetic or regenerative applications (an autologous procedure). This simplification of fat stem cell therapy is extremely important because it brings the technology to a greater range of patients at a reduced cost with less processing intervention resulting in reduced regulatory requirements.

Caution is Needed

There is however a cautionary tale. There were 3 patients in Florida who were blinded after taking part in a 'clinical trial' using fat stem cells. These patients were enrolled into a 'clinical trial' run by the company involved and they were each asked to pay $5000 to take part in the trial. This request for payment should have rung a multitude of alarm bells because clinical trial volunteers should ***never be asked to pay to take part in the trial***. These unfortunate patients clearly did not know this and either ignored advice or made the mistake of not taking advice at this stage. *Always* take unbiased, independent advice if you are thinking of taking part in a clinical trial. These unfortunate people joined the 'clinical trial', paid their money, and received injections of their own 'processed' adipose stem cells into both eyes. The fact that they received treatments into both eyes at the same time is quite shocking. Even experienced ophthalmologists only treat one eye at a time to minimise unanticipated complications in both eyes and once again if the patients had taken advice then they would have had this fact highlighted. The outcome was that these three patients became permanently blind. This is a shocking example of malpractice in the stem cell industry. It also illustrates the extreme vulnerability of some patients who, in their desperation, can easily be drawn into a procedure which is dangerous and unproven.

Clinical Trials and 'Freeze Young'

Despite this horror story, adipose (fat) stem cells do have enormous potential when used properly either in tried and tested applications or in clinical trial. The 'tissue forming' stem cells found in adipose tissue could be particularly useful in

CHAPTER 9

A Human Touch

(The development and use of induced pluripotent stem cells)

Nothing eases suffering like a human touch.
Bobby Fischer

Summary: This chapter describes the development and potential applications of man-made stem cells called induced pluripotent stem cells (iPSC). The technology involved and the possibilities for research and therapy are described.

MAN-MADE

All of the stem cell achievements, advances, and disappointments so far described in this book have been made using human intuition, knowledge, determination, and sometimes good luck. The stem cells which have been described are all naturally occurring and their use has been a matter of discovery and clinical utilization. This has brought us to the point where we have considerable and increasing knowledge in stem cell technology, but there is clearly much more to be done.

This chapter considers a new type of stem cell, which is man-made. It is called an induced pluripotent stem cell (often called iPSC) and it is a 'tissue forming' stem cell capable, in theory, of producing all tissue types in the body similar to the properties of embryonic stem cells. This is why it has the term 'pluripotent' in its' name. This means that it can, in theory, make all of the tissues of the body. In order to create iPSC, researchers took the unusual step of making their starting point a natural skin cell. Skin cells can be obtained very easily either by a very quick and painless biopsy or even by a simple swab of the inside of the cheek. Even though there are stem cells in the skin itself (these skin stem cells regenerate the skin on a daily basis), it is not these stem cells which were of interest. The purpose is to obtain a normal cell which was easy to obtain and manipulate, making skin the obvious candidate. Many workers have since used blood cells as the starting point for iPSC, which is arguably easier than using skin. Once the sci-

entists had the starting point of normal human skin or blood cell, the next challenge was to treat this cell to make it transform from a normal skin or blood cell to a 'tissue forming' stem cell. This transformation was achieved by using an 'inactivated' virus to introduce 4 new genes into the skin or blood cell. These 4 genes resulted in the cell changing from normal skin or blood to a 'tissue forming' stem cell.

This work caused great excitement in the stem cell community (so much excitement that the scientists involved were awarded a Nobel prize) because it meant that any patient needing 'tissue forming' stem cells for treatment could have them 'manufactured' on demand from their own normal tissue cells, in theory.

Good or Bad?

The production of iPSC, at first, sounded like the ultimate stem cell solution to the Regeneration Promise but it soon became clear that such manipulation of cells might not be quite as attractive. Two specific concerns were raised by many scientists; these are:

The use of a virus to introduce new genes into skin or blood cells. People question whether the virus could place the 4 new genes in the correct place in the skin or blood cell and if the genes went into the wrong place, then would there be unforeseen problems? The answer, at present, to this question is that we do not really know but great caution is recommended. Any procedure which involves changing, replacing, or adding genes into a cell is potentially risky.

The second criticism relates to the 4 genes themselves. Some of the genes used were genes known to be associated with malignant cancerous cells. The worry was that if these genes are introduced into normal cells, could they, at some point, form malignant cells? The answer, at present, is that the genes associated with malignant cancerous cells should be avoided where possible and many workers have developed alternative genes that enable iPSC development but are not associated with malignant disease. Once again, great caution is recommended.

Despite these concerns, research and development work has continued on iPSC with the development of different gene delivery systems and some workers even used different genes to create iPSC. These two changes began to make iPSC more readily accepted but the creation of iPSC is still controversial. This controversy becomes even stronger when the potential for clinical use of iPSC is discussed. For this reason, iPSCs have stayed in the research laboratory, rather than going immediately to a clinical trial, in order to properly assess their safety. If iPSCs

eventually come into routine clinical use, then it will only be thorough clinical trials, to show evidence of safety and efficacy, which will ideally be carried out on a global multi-center scale.

Organoids

Despite the concerns surrounding the clinical use of iPSC, the use of these man-made stem cells in research has continued and is starting to show some very interesting possibilities.

One particular development in iPSC 'tissue forming' stem cell technology has been to use them as the basis for a technology called organoids. Organoids are created by first creating some iPSC as described above and then driving these iPSCs (using known chemicals and stimulatory molecules) to produce specific tissues, such as kidney, nerve or liver. The resultant tissue cells produced from iPSC start to cluster together to produce tiny versions of the organs they represent and this is known as an organoid. Organoids have several potential uses, such as the study of disease processes in organs, screening of pharmaceuticals, and even possibly, some role in therapy in the future, although there is still an enormous amount of work to be done before any therapeutic applications of iPSC organoids become a reality. It is possible, maybe even likely, that this may never happen.

Organoids which develop into testicular or ovarian tissue have been proposed as a potential source of gametes (sperm and eggs) to treat infertile patients. At present, this is just an interesting concept largely because of the extremely complicated biological and ethical issues raised by such a proposal. It could, for example, be possible to make testicular and ovarian organoids from the same person, obtain sperm and eggs and create an embryo and put this embryo back into the original cell donor (assuming that she was female). This kind of proposal raises so many concerns and objections that it is never likely to happen. This is a good thing.

It would even be theoretically possible to do this process to create iPSC derived sperm and eggs using a donor who has already gone through menopause or suffered an early menopause. Such ideas are wild, untested concepts at the moment, but if the technology develops, we may soon be faced with ethical dilemmas, about firstly, should research be allowed and secondly, should such technology be used in clinical practice? My thought at the moment is a clear 'no' to both of these questions, but only time will tell.

Clinical Trials

At the time of writing, there were 19 clinical trials recruiting volunteers using iPSC as the basis of the trial. These clinical trials cover a wide range of

CHAPTER 10

Baby is Back!

(A review of cord tissue, placenta, and amniotic fluid/membrane stem cells)

What good mothers and fathers instinctively feel like doing for their babies is usually best after all.
Benjamin Spock

Summary: This chapter reviews the stem cells, which have been discovered in the tissues related to pregnancy, such as the umbilical cord, placenta, and amniotic fluid and membranes, which surround the baby in the uterus. These stem cells are not in routine clinical use, but some clinical trials are underway, which may give us important safety and efficacy information in the future.

STEM CELLS IN TISSUES RELATED TO PREGNANCY

Back in Chapter 3, the development of cord blood stem cell technology and how it has resulted in a great alternative source of 'blood forming' stem cells to treat blood disorders was described. As a result of this excellent work, it soon became apparent that other tissues associated with pregnancy are also potential sources of 'tissue forming' stem cells. These stem cells in tissues related to pregnancy have great potential but also some great challenges.

Umbilical Cord Tissue

The first of these tissues, which were investigated, was the umbilical cord itself, generally known as 'cord tissue'. Cord tissue has been found to contain 'tissue forming' stem cells with the potential to treat a range of diseases already described for 'tissue forming' stem cells. This discovery led private cord blood banks to offer the collection, processing, and storage of cord tissue stem cells to their clients who were already collecting and storing cord blood stem cells. At present, almost all private cord blood clients in the UK and overseas offer to collect and store cord tissue at the time of birth to their clients. The process of collection and storage of cord tissue is easy and it can be carried out by the phlebotomist who collected the cord blood.

Following birth and cord blood collection, a small length of the umbilical cord (usually about 10 cm) is cut and placed into a collection pot provided in the cord blood collection kit. The collection pot contains saline supplemented with antibiotics to minimize bacterial growth in the collected tissue. The cord tissue is then sent to the private cord blood bank laboratory, along with the cord blood, for processing and storage. This, of course, makes more money for private cord blood banks per client and it arguably provides another source of 'tissue forming' stem cells for use in the family. There are, however, some problems with this cord tissue service that rotate around the type, number, and clinical usefulness of cord tissue stem cells.

There is still considerable debate in the scientific community about the nature and number of 'tissue forming' stem cells in the cord tissue. This technical argument is of little interest to the general reader but the outcome of the discussions is that not even the scientists are sure of the type, number, and possible clinical applications of 'tissue forming' stem cells in the cord tissue. This raises questions about the actual potential use of these stem cells and whether or not paying to store them is advisable. The private cord blood banks have, not surprisingly, convincing marketing on this subject but it seems that this marketing bears little resemblance to the current scientific knowledge and evidence. The collection and storage of cord tissue, in parallel with cord blood collection, represents a significant new income source for private cord blood banks. The only people likely to benefit, in the short term at least, are therefore the private cord blood banks.

There is also some variation in the way in which private cord blood banks process and store cord tissue. This could have a big impact on the way in which it might be used in the future. Some private cord blood banks simply cut a small length of the umbilical cord (1-2 cm) into smaller pieces of tissue and freeze the pieces. Other private cord blood banks may process the cord tissue to extract the cord tissue 'tissue forming' stem cells using enzymes and freeze these stem cells. The latter is much cheaper for the cord blood bank than the former and therefore, most cord tissue is stored in small pieces rather than frozen stem cells. This means that if the stem cells are needed, then the tissue must then be thawed and processed to extract the stem cells, which potentially means that the resultant stem cells might be of poor quality or even unsuitable for clinical use. It must also be noted that cord tissue processing to extract stem cells requires the use of enzymes (these are chemicals which speed up biological reactions) to separate the stem cells from the rest of the cord tissue. This, therefore, involves significant manipulation in the eyes of the regulators, which makes the final clinical use of cord tissue stem cells less likely and more expensive to achieve.

Another potential problem with cord tissue 'tissue forming' stem cells is that they are found in relatively low numbers when the cord tissue is broken down using enzymes. This means that to use cord tissue stem cells in any clinical application will almost certainly need an expansion of the cell numbers in the laboratory in order to provide a therapeutic dose. Such expansion is once again another significant manipulation of the cells resulting in increased regulation and increased production costs.

At present, it seems unlikely that cord tissue stem cells will be useful in any routine clinical application in the near future. If they do prove useful, then their preparation for clinical use will be an expensive, time consuming process, and the effort would have to justify the outcome. It would, at present, be much easier to just use fat stem cells. These are readily available and arguably more effective. Despite all of this, private cord blood banks continue to promote the collection and storage of cord tissue and clients continue to pay for the service!

Clinical Trials of Cord Tissue Stem Cells

In terms of the potential clinical applications of cord tissue 'tissue forming' stem cells, there were, at the time of writing, only 4 clinical trials recruiting volunteers using cord tissue stem cells. All four of these clinical trials are looking at diseases which could just as well use 'tissue forming' stem cells from other sources, such as adipose tissue. Therefore, even for clinical trials, these cord tissue stem cells may already be obsolete. On balanced collection and storage of cord tissue, at the time of cord blood collection, is *not worth the investment and private cord blood clients should refuse this service if it is offered*. Public cord blood banks do not collect, process, and store cord tissue for clinical use. If, in the future, the proven clinical utility and safety of cord tissue 'tissue forming' stem cells is demonstrated, then the public cord blood banks could easily begin collection, processing, and storage. I doubt that this will ever happen unless there is a quantum leap in our understanding and use of cord tissue stem cells.

Placenta Stem Cells

The placenta is a complex organ which supplies nutrients and oxygen to a developing baby and removes waste products and carbon dioxide. It functions for the whole of the pregnancy and once delivered after the birth of the baby, it is almost always discarded as medical waste. It has long been part of human cultural and ethnic ceremonies and beliefs, especially in Africa, and indeed some animals will eat the placenta following birth as an important source of nutrients. However, this is not recommended in humans.

CHAPTER 11

Kill or Cure?

(The Controversies Behind Offers of Treatment Made by Stem Cell Companies)

The best cure for insomnia is to get a lot of sleep.
W.C. Fields

Summary: This is perhaps the most important chapter in this book because it offers guidance and advice to patients considering treatment at a private clinic using stem cells and related regenerative medicine technology. This chapter provides information which may help in preventing a lot of pain, suffering, disappointment, and losing a lot of money to rogue stem cell clinics for untested and unproven stem cell-based 'treatments'.

STEM CELL TREATMENTS (*CAVEAT EMPTOR:* BUYER BEWARE*)*

In this book, I have focussed on different stem cell types and on the potential and pros and cons of using these stem cells to treat a very wide range of diseases. There are many pitfalls to avoid stem cell technology, but there are also some promising and exciting ideas, especially at the level of basic laboratory research and future therapies.

There are clearly tried and tested stem cell therapies, such as those involving bone marrow 'blood-forming' stem cells, which have been described in detail. Equally, there are others where the routine clinical applications are either uncertain or even possibly unsafe. The purpose of the previous Chapters was to provide a clear, unbiased opinion on what is currently happening in stem cell technology and regenerative medicine today and empower the reader who may be undergoing or considering undergoing stem cell therapy to remain safe both medically and financially. I hope that I have succeeded to this point and that all readers remain medically and financially safe!

The Regeneration Promise

This chapter is very different and extremely important in the overall discussion of the Regeneration Promise. I now intend to offer specific guidance and advice to

anyone considering paying for stem cell treatment for any disease either in your own country, overseas or offshore. There are many private companies worldwide offering stem cell treatments. They are often either located offshore, or in unregulated mainland Countries, and this is usually to avoid the regulatory issues which would otherwise impede their 'treatment' offerings.

These companies typically offer 'treatment' to patients who are most commonly suffering from terminal, degenerative or life-changing disease with no known cure in current medicine. Such potential patients may also be suffering from a debilitating chronic (long-term) disease (for example, diabetic ulcers) with an ineffective treatment in current medicine. Such clinics often list an amazing number of different diseases which they have 'treated' using their technology and support these claims with patient testimonials. This should be seen as the first warning sign. My advice here is that potential patients must be *very* sceptical about such claims and to discuss them with a *trusted* unbiased physician or clinical scientist *before* agreeing to *any* type of treatment.

There are some very important points to consider and to be very cautious about when you are considering a private stem cell clinic:

If a stem cell company claims that one type of stem cell can treat a wide range of diseases (apart from bone marrow stem cells and blood diseases), then this is at best questionable and at worst irresponsible. They are knowingly trying to mislead. If you see this being promoted by a company, then walk away. There is nothing in the current medical information from clinical trials or basic research, which suggests this wide scope of stem cell technology. Stem cell types, if anything, are disease-specific. Remember: 'The right stem cell for the right job delivered to the right place'.

If a stem cell company uses patient or celebrity testimonials about their 'treatments', then be extremely cautious about what you believe. Patient or celebrity testimonials may either be fact or fiction (this is impossible to properly assess), and they are most likely to be fiction. Even with an enormous benefit of the doubt, these anecdotal testimonials have little or no relevance or value. Such testimonials (if they are genuine) are simply descriptions of treatment and outcome in an unregulated single treatment event. This does not mean that the treatment discussed is either safe or effective, and it certainly does not recommend that treatment to you. An unethical company (yes, there are unethical stem cell companies!) could even hire actors to make these testimonials, and the viewer has no way of knowing whether it is truth or hoax. Such anecdotal patient testimonials are generally considered to be irrelevant by the medical and scientific community because any beneficial effect maybe just a

coincidence or a spontaneous 'cure' of the disease or the placebo effect or, worse still, a lie. The placebo effect is when a treatment seems to provide benefit even when the active ingredient is removed. It is not well understood and may have a psychological basis. In summary, do not be impressed by patient testimonials under any circumstances. *They cannot be trusted* to be true or relevant to any response you might have to the same 'treatment'.

Many patients who may be considering stem cell therapy have quite often been through treatments in current medicine, which have either failed or have been ineffective. This means that these patients are very vulnerable. They seek a solution to their problem and many will do anything, including paying large amounts of money, to get access to these 'stem cell or regenerative medicine cures'. This was sadly demonstrated in the recipients of adipose stem cell 'treatment' described in Chapter 8, which resulted in blindness.

If you do decide to talk to a stem cell clinic with a view to some sort of treatment using stem cells and related technology, then there are some key points which you need to be very clear about before proceeding with any agreement; these are:

You need to trust the clinic you propose to use. This will require you to be critical of *everything* they say and if you do not get satisfactory answers, then do not hesitate to walk away. You should only trust people who are properly qualified and competent to provide healthcare advice. There are many scams and fake qualifications available, which may, at first glance, look impressive but on closer inspection can be either fake or meaningless. You should also assure yourself that not only the 'front-line' people are properly qualified but also those people who support the overall operations in the clinic. If the 'front line' person is a salesman, and the Board consists of businessmen, then be very wary. This means that the clinic is more interested in profit than offering a safe and effective treatment. Please also bear in mind that companies can put almost anything they want to on their own websites, including 'patient' testimonials and 'we are the best'. This information is meaningless and unreliable. If a clinic boasts about being the 'best' then it is a good bet that they are not. Healthcare professionals who are good at their job do not boast that they are the best and that their clinic is better, in fact, they are often the most modest people you can meet. The clinic also needs to have published peer-reviewed publications in medical journals and *unbiased* third party reviews to show that they are professional and trustworthy.

The subject of money has come up several times in this book. I do not like talking about money and health care, but many people do. Unfortunately, stem cell technology and regenerative medicine is viewed as a simple route to profit by some people. The global regenerative medicine industry is estimated to be

CHAPTER 12

A Final Thought

(Ideas on cutting edge technology)

Imagination is more important than knowledge. Knowledge is limited. Imagination encircles the world.
Albert Einstein

Summary: This final chapter in this book provides an overview of what is happening at the cutting edge of stem cell and regenerative medicine technology. It describes the research currently underway and how these technologies may have an impact on future clinical practice for all of us. Some of the ideas mentioned here will not be in the public domain, but they are all valid research projects.

SOME THINGS WORK SOME THINGS DO NOT

This is the exciting bit! I can now tell you about some of the amazing ideas for the future of stem cell technology and regenerative medicine. These ideas are all on the very cutting edge of science and medicine and involve concepts which are new, innovative, and sometimes controversial. It is, however, very important to describe these concepts and research because many of them will no doubt find their way, *via* proper evidence-based research and clinical trial, to routine clinical practice in the future. Some of the ideas may fall along the wayside as interesting academic ventures which come to nothing from a practical point of view. This is how all research develops and is not unique to stem cell technology. In science, some things work, some things do not work. If everything works, then that rings many scientific alarm bells. This is the same way that claims about one type of stem cell treating many diseases rings alarm bells. The only exception to this rule is the bone marrow 'blood-forming' stem cell, which can treat 80 different blood disorders. These 80 diseases represent blood disorders and are therefore, one specific group of diseases. It is no surprise that 'blood-forming' stem cells can treat blood disorders.

A mention of any of the technology below *does not* mean that it is either proven or safe, and anyone considering using any of these technologies should initially

get advice from a trusted, unbiased physician or clinical scientist before even considering using the technology. This general rule applies to any technology and therapy which has not been thoroughly tested to prove its safety and effectiveness and the aim is to protect people from unsafe and unproven treatments. The technologies are presented in no particular order and an opinion on future importance and possible actions needed for each technology is offered.

Cord Blood Transfusion

In Chapter 3, I described the use of umbilical cord blood as a source 'blood-forming' stem cells to treat leukaemia and blood disorders. Cord blood stem cells are a safe and effective treatment for blood disorders, especially in children. Cord blood can, in fact, also be used in transfusion as a supplement, or alternative to donated adult blood. Donated adult blood is what is commonly known as a blood transfusion around the World.

When cord blood is used for blood transfusion, it can:

reduce inpatient hospital times
allow faster recovery and reduce hospital-based deaths for patients suffering from accidents, acute and chronic disease and terminal illness
Promote a quicker recovery in patients who have had major surgery.

Cord blood transfusion was pioneered by my friend and colleague, Professor Niranjan Bhattacharya, at the Kolkata School of Tropical Medicine.

Umbilical cord blood contains three critical substances which make it much more effective for blood transfusion than donated adult blood, these are:

Fetal haemoglobin: This is the protein in our red blood cells which carries oxygen. The fetal haemoglobin in cord blood red cells can carry more oxygen than the haemoglobin in donated adult blood red cells. This means that a recipient of a cord blood transfusion, therefore, has higher oxygenation rates than the recipient of donated adult blood. This could be critical in severe illness, trauma, or during and after surgery where patients often suffer from low oxygen levels.
Cytokines (proteins) which are not present in donated adult blood. These can reduce the damage caused by trauma and disease and promote faster recovery rates for these patients
Stem cells (both blood-forming and tissue-forming) may help to repair damaged tissue in both accidents and disease

Cord blood for transfusion would be collected as described in Chapter 3 and grouped (using the standard ABO blood group system) and screened for infectious disease in the same way as donated adult blood. Most Countries have the infrastructure needed for this process.

Professor Bhattacharya has carried out hundreds, possibly now thousands, of cord blood transfusions in India and found no adverse effects at all in these recipients. We must not ignore this priceless resource and related technology. At present, 99% of potential cord blood donations are discarded as medical waste and we should, in my opinion, start to think about cord blood not only for transplantation but also for transfusion.

Most major hospitals have a labour ward, and they have lots of patients who need blood transfusion. Such hospitals also have A&E and surgical or oncology departments with constant demands for blood for transfusion. Cord blood could be collected in the labour ward and then easily used as a reliable and effective transfusion product for their patients in the same hospital. A large labour ward could potentially provide the transfusion needs for the whole hospital and even more.

NHSBT (the blood and transplant section of the NHS) and equivalent organizations globally often warn of donated adult blood shortages; these are mainly seasonal shortages. This approach to the collection of cord blood for transfusion could not only remove these shortages but also save the health care providers a considerable amount of time and money and reduce a significant amount of suffering in our patient population.

Using cord blood for transfusion is a fantastic idea, but as with all of these ‘cutting edge’ technologies, we must proceed with caution to ensure that no one suffers along the way. The next step is to bring cord blood transfusion into use in a small number of patients (a phase I clinical to trial) to ensure safety, and if this turns out to be so (which is what Professor Bhattacharya has already shown), then the technology could then be brought into general use in Phase II multi-center clinical trial. If we can bring umbilical cord blood transfusion into routine clinical practice it could be a lifesaver and it could also revolutionize the way in which we understand and use blood transfusion.

Cord blood transfusion could also be extremely useful in Countries where the infrastructure for adult blood donation is either poor on non-existent. In this context, I am currently working with colleagues in Nigeria to bring cord blood transfusion to Nigerian hospitals.

GLOSSARY

Autologous: This is a treatment where cells or tissue are taken from a patient processed and returned to the same patient

Allogeneic: This is a treatment where cells or tissue are obtained from a donor and given to an unrelated recipient. The donor cells are often frozen before use.

'Blood Forming' Stem Cells: These are stem cells found in the bone marrow and cord blood. Bone marrow blood forming stem cells can be mobilised into the circulation as peripheral blood stem cells using medication for easier collection. The scientific name for these stem cells is haemopoietic stem cells.

Cell Programming: This is technology which can enable the transformation of normal body cells (*e.g.* skin cells) directly into the cells needed for treatment (*e.g.* heart cells) by introducing the precise growth factors and genes needed for the direct cell transformation. This is a refined form of induced pluripotent stem cells which instead of going to the stem cell state the method allows direct transformation to the target cell state.

Cord Blood Stem Cells: These are blood forming stem cells which can be isolated from the blood remaining in the umbilical cord and placenta at the birth of a baby.

Cord Blood Transfusion: This is the use of whole cord blood collected at birth as an alternative or supplement to donated adult blood. Cord blood transfusion may have benefits over adult blood transfusion and could be used in parallel to adult blood transfusion.

Cord Blood Transplantation: This is the process by which cord blood stem cells are used to treat blood disorders.

Cord Blood Unit: A cord blood unit is the frozen stem cells collected from a cord blood collection which are stored frozen in liquid nitrogen in a bag about the size of a credit card. The cord blood unit is what is sent frozen to the hospital for transplantation.

Dental Pulp Stem Cells: These are the 'tissue forming' stem cells found inside baby and adult teeth. The stem cells can be collected and frozen for later use.

Fat (adipose) Stem Cells: These are stem cells found in fat (*e.g.* fat from the abdomen). They are known scientifically as adipose stem cells and they are 'tissue forming' or mesenchymal stem cells.

Haemopoietic Stem Cells: This is the scientific name for 'blood forming' stem cells found in bone marrow and cord blood.

Human Tissue Authority (HTA): This is the UK regulatory authority which regulates the use of human cells in procedures such as bone marrow transplantation and cell therapy

Induced Pluripotent Stem Cells: These are 'man made' stem cells created by inserting new genetic material (genes) into normal body cells such as skin cells.

Mesenchymal Stem Cells: This is the scientific name for 'tissue forming' stem cells.

Organoids: These are tight ball like collections of cells derived from induced pluripotent stem cells, which can be formed into most tissues of the body. They provide a potential system to study development, organ physiology and possible drug testing.

Public Cord Blood bank: This is a cord blood collection processing and storage facility usually run by a healthcare provider *e.g.* in the UK the NHS Blood and Tissue Service (NHSBT). These organisations collect cord blood, process it and store it and make it available to anyone in need. The donor does not pay for this process and the public cord blood bank will charge the recipient hospital when providing a cord blood unit for transplant.

Pluripotent Stem Cells: These are stem cells found in developing human and animal embryos, which have the potential to form all tissues in the body.

Private Cord Blood Bank: This is a company which provides cord blood collection processing and storage for family use only and an initial fee and an annual storage fee is paid for this service.

Teeth Stem Cells: These are stem cells found inside adult and infant teeth which can be collected and stored frozen. Teeth cells (known scientifically as dental pulp stem cells) are 'tissue forming' or mesenchymal stem cells.

Telomere: A portion of DNA on the end of each chromosome which reduces as the cell divides and undergoes ageing.

'Tissue Forming' Stem Cells: These are stem cells found in the umbilical cord tissue placenta, fat and teeth. They are also present, but in lower numbers, in bone marrow. They are known scientifically as mesenchymal stem cells.

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Peter Hollands

Peter was trained at Cambridge University, at Churchill College, and completed his Ph.D. under the supervision of Professor Sir Bob Edwards, FRS who was awarded the Nobel Prize for his work on IVF. Bob Edwards, a pioneer in stem cell technology, was the key inspiration for Peter to work in the field of stem cell technology. Peter has worked at Bourn Hall, the first-ever IVF clinic, and has worked on both IVF and Regenerative Medicine for over 40 years in the private and public sector. He has also been working at several UK Universities carrying out undergraduate and postgraduate teaching and research on stem cell technology. Peter has also worked in the UK, Europe, Canada, and Nigeria and holds a visiting Chair in Regenerative Medicine from the University of West Bengal in recognition of his work with colleagues in Calcutta. He now lives in rural Cambridgeshire.