


Based in part on the proceedings of the Newborn Stem Cell Advisory Meeting, an international gathering of obstetricians/gynecologists, transplant experts, and researchers convened on April 6, 2006, at the Cord Blood Registry Laboratory and Processing Facility in Tucson, Arizona.

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Emerging stem cell therapies

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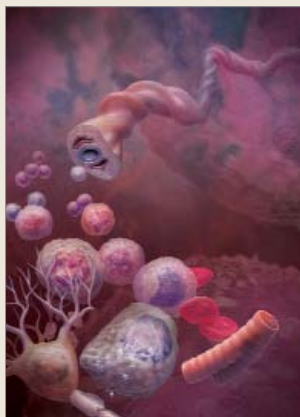
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Emerging stem cell therapies

The role of cord blood banks

CONTENTS

Introduction BRUCE K. YOUNG, MD	S3
Stem cells: An overview	S5
Newborn stem cell transplantation: The medical literature	S7
Emerging applications for newborn stem cells	S10
Practical issues for clinicians: Cord blood collection and patient counseling	S15
Profile of a family bank: Cord Blood Registry	S16



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GUEST EDITOR AND SYMPOSIUM ADVISOR

Bruce K. Young, MD

Professor of Obstetrics and Gynecology
New York University School of Medicine
Silverman Professor of Obstetrics and Gynecology
Director, Fetal Therapy Program
New York University Medical Center
Emeritus Director, Division of Maternal-Fetal Medicine
New York University Medical Center, Tisch and Bellevue Hospitals
New York, New York

ADVISORS AND CONTRIBUTORS

James E. Baumgartner, MD

Associate Professor
Department of Neurosurgery
Division of Pediatric Neurosurgery
University of Texas Health Science Center at Houston
Houston, Texas

Ning Chen, MD

Department of Neurosurgery
Center of Excellence for Aging and Brain Repair
University of South Florida
Tampa, Florida

Charles Cox, Jr, MD

The Children's Fund Distinguished Professor of Surgery and Pediatrics
University of Texas Medical School at Houston
Houston, Texas

Michael Haller, MD

Assistant Professor
Pediatric Endocrinology
University of Florida
Gainesville, Florida

Joshua M. Hare, MD

Professor of Medicine and Biomedical Engineering
Director, Heart Failure and Cardiac Transplant Program and CV Section
Johns Hopkins Institute for Cell Engineering
The Johns Hopkins University School of Medicine
Baltimore, Maryland

David T. Harris, PhD

Professor, Department of Microbiology and Immunology
University of Arizona-Tucson
Tucson, Arizona
Scientific Director, Cord Blood Registry
San Bruno, California
Tucson, Arizona

Colin P. McGuckin, DPhil

Professor of Regenerative Medicine
North Eastern Stem Cell Institute and Center for Cord Blood
Newcastle University
Newcastle-upon-Tyne, United Kingdom

Arnon Nagler, MD, MSc

Professor of Medicine
Director, Division of Hematology, Bone Marrow Transplant and Cord Blood Bank
Chaim Sheba Medical Center
Tel Hashomer, Israel

Richard H. Schwarz, MD

Vice Chairman for Clinical Affairs
Department of Obstetrics and Gynecology
Maimonides Medical Center
Professor of Obstetrics, Gynecology and Reproductive Science
Mt. Sinai School of Medicine
Brooklyn, New York

Introduction

Over the past decade, the controversy surrounding embryonic stem cell research has dominated the headlines. Despite this, many people remain unaware of human umbilical cord blood and other noncontroversial stem cell sources that are routinely used in medical treatments. Immense confusion remains about the different sources of stem cells and their use—in the minds of the government, the public, and the medical community. Today, cord blood and bone marrow share a growing number of clinical uses. A federal program created in 2005 will increase the national cord blood inventory. However, since 1992, family cord blood banks have provided collection, processing, and preservation services for those who elect to reserve a newborn's genetically-related stem cells for their family's use. Some have questioned the necessity of family cord blood banking, citing the number of clinical applications, but recent advancements validate the importance of this practice. A growing number of medical treatments, including regenerative therapies, utilize the newborn stem cells (NBSC) in cord blood. Within the context of exploding research in NBSC, family banking is growing in popularity—and scientific credibility.

This monograph includes a stem cell primer to clarify the issues associated with the 3 primary stem cell sources. It also features articles that explain the current and emerging clinical applications of the NBSC found in cord blood.

This publication is based in part on the April 2006 Cord Blood Stem Cell Advisory Meeting, which brought together physician-scientists from The United Kingdom, Israel, and several American universities, who are studying the potential use of NBSC to treat many difficult medical problems. The meeting was designed to enhance the current state of knowledge about cord blood stem cells among scientists, clinicians, and the general public. The publication of these proceedings is intended to clarify some of these issues for our clinical colleagues and facilitate discussion of this exciting new field of medicine with patients.

Many people, including medical professionals, are eager to learn more about NBSC banking, yet they are unaware of recent regenerative medicine research or the many diseases that are currently treatable with stem cells. Pregnant women, who ultimately decide the fate of their newborn's stem cells, frequently look to their clinicians for guidance in evaluating their options. Furthermore, many health care professionals are unaware of the federal legislation to estab-

lish nationwide cord blood banks. They have never initiated a discussion with a patient about cord blood banking and are unprepared to answer an expectant mother's questions. As more pregnant women become aware of the importance of cord blood stem cells, it is increasingly necessary for clinicians to be well informed.

Decades of development and use

Human umbilical cord blood stem cells have been used to treat blood disorders, cancers, immunodeficiencies, inborn errors of metabolism, bone marrow failure syndromes, and some autoimmune conditions.¹ They are indicated for many of the same conditions that are treated with bone marrow, but they are associated with decreased risk of transplant complications and increased rates of matching HLA antigens. Uses of NBSC will undoubtedly expand as researchers investigate their application in regenerative medicine.

Emerging applications and regenerative medicine

The field of stem cell research is increasing exponentially and encompasses a wide range of topics—from deepening our understanding of cellular development to applying these findings to repair and create organs. Fundamental to the use of any stem cell therapy is a clear understanding of the immunology for allotransplantation as well as autotransplantation for malignancies and immunologically mediated diseases such as diabetes and systemic lupus.

Scientists are using stem cells to develop therapies for heart disease, cancer, stroke, spinal cord injury, autoimmune diseases, and regeneration of bone, cartilage, and eye tissue. These efforts are being pursued by academic centers for stem cell research across the United States and abroad. Many corporations recognize the potential future economic value of cell therapy and have partnered with academic centers to sponsor research, education, and scientific meetings to disseminate information, share ideas, and encourage collaboration.

New legislation and medical practice

In December 2005, Congress passed the Stem Cell Therapeutic and Research Act, designating \$79 million to

► Introduction

collect sufficient units of cord blood stem cells to provide a suitable match for 90% of the Americans who might need stem cells.²

Clearly, these developments raise critical issues relating to patient counseling: All pregnant women should know they have the option of collecting and storing NBSC. Family banking (also known as private banking) provides immediate access to genetically related stem cells, which increases the chance of HLA antigen matching compared with public registries and improves transplant outcomes compared with cells from unrelated donors. Furthermore, family banks provide access to autologous stem cells, which are being evaluated in clinical trials as therapies for diabetes, traumatic brain injury, and myocardial infarction.

Conversely, public banks provide allogeneic NBSC that are available to HLA antigen-matched individuals through a searchable database. Because the number of available samples affects the odds of finding an HLA antigen match, the federally supported national program has enormous potential for the future.

As a community service, many family banks provide processing and storage at a nominal cost if a family member is diagnosed with a condition treatable with stem cells. This information should be provided to all expecting mothers.

The presentations at the Cord Blood Stem Cell Advisory Meeting on which this publication is based address the role of NBSC in neurological conditions, diabetes, heart disease, transplantation immunology, regenerative medicine, and hematopoiesis. Summaries of these presentations and discussions among researchers and clinicians are featured in this publication.

The meeting attendees also discussed how pediatricians and obstetricians should advise patients about cord blood as a stem cell source, which is plentiful, easily collected, and not controversial. Stem cell therapy will be a cornucopia of benefits to humanity, virtually unlimited in its future potential. That future begins now.



Bruce K. Young, MD

Silverman Professor of Obstetrics and Gynecology
New York University Medical Center
Guest Editor and Symposium Advisor

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Stem cells: An overview

The proposed use of embryonic stem cells has produced much controversy in the lay press. However, bone marrow and human umbilical cord blood (HUCB) routinely provide stem cells, also known as newborn stem cells (NBSC), for medical therapies and research. Adult bone marrow stem cells, NBSC, and embryonic stem cells differ greatly in terms of their characteristics, status of research, and their current and potential utility in the treatment of life-threatening illnesses and chronic conditions (TABLE 1). Because they can only be obtained at birth, current and emerging research using NBSC has important implications for women who are pregnant or contemplating pregnancy, and their families. A thorough understanding of NBSC applications is integral in deciding to collect and either store or donate cord blood. The types of stem cells available are reviewed in TABLE 2.

Adult stem cells that form blood and the immune system are found in bone marrow, and have been used for over 40

years. Researchers are now finding applications in regenerative medicine. In the future, stem cells may be used to treat neurodegenerative disorders and organ damage. Adult stem cells from bone marrow have significant limitations: Successful treatment requires either autologous cells or donor cells that have HLA antigens compatible with those of the recipient. Exact matches can be difficult to obtain; siblings have only a 1 in 4 chance of a perfect HLA antigen match. In a 1997 report, investigators noted that worldwide registries include more than 10 million adult donors. Still, only 50% of Caucasian patients will find a suitable bone marrow match.¹ Ethnic minority groups remain underrepresented in registries, which could decrease the odds of finding a suitable transplant match and therefore put these populations at risk.

Umbilical cord blood, long considered a “waste product” in the delivery process, is a rich source of hematopoietic stem cells. At present, cord blood stem cells are used to treat more

TABLE 1

Indications for cord blood transplant

Oncologic disorders

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Autoimmune lymphoproliferative syndromes
- Burkitt lymphoma
- Chronic myeloid leukemia
- Cytopenia related to monosomy 7
- Familial histiocytosis
- Hemophagocytic lymphohistiocytosis
- Hodgkin's disease
- Juvenile myelomonocytic leukemia
- Langerhans cell histiocytosis
- Lymphomatoid granulomatosis
- Myelodysplasia syndrome
- Non-Hodgkin's lymphoma

Hematologic disorders

- Amegakaryocytic thrombocytopenia
- Autoimmune neutropenia
- Congenital dyserythropoietic anemia
- Congenital sideroblastic anemia
- Cyclic neutropenia
- Diamond Blackfan anemia
- Evan's syndrome

- Fanconi anemia
- Glanzmann's disease
- Hypoproliferative anemia
- Juvenile dermatomyositis
- Juvenile xanthogranulomas
- Kostmann's syndrome
- Pancytopenia
- Red cell aplasia
- Refractory anemia
- Severe aplastic anemia
- Shwachman syndrome
- Severe neonatal thrombocytopenia
- Sickle cell disorders
- Systemic mastocytosis
- Thalassemias
- Thrombocytopenia with absent radius

Immune deficiencies

- Ataxia telangiectasia
- Cartilage-hair hypoplasia
- Chronic granulomatous disease
- DiGeorge syndrome
- Hypogammaglobulinemia
- IKK gamma deficiency
- Immune dysregulation polyendocrinopathy

- Mucopolipidosis, Type II
- Myelokathesis
- Severe combined immunodeficiency
- Wiscott-Aldrich syndrome
- X-linked agammaglobulinemia
- X-linked immunodeficiency
- X-linked lymphoproliferative syndrome

Metabolic disorders

- Adrenoleukodystrophy
- Alpha mannosidosis
- Gaucher's disease (infantile)
- Globoid cell leukodystrophy
- Gunther disease
- Hermansky-Pudlak syndrome
- Hurler syndrome
- Hurler-Scheie syndrome
- Hunter syndrome
- Maroteau-Lamy syndrome
- Metachromatic leukodystrophy
- Mucopolipidosis Types II, III
- Neimann Pick syndrome, types A and B
- Sandoff syndrome
- Sanfilippo syndrome
- Tay Sachs disease

Adapted from Moise KJ Jr. *Obstet Gynecol.* 2005;106:1393-1407.

TABLE 2
Stem cell sources

	ADVANTAGES	DISADVANTAGES
Adult	<ul style="list-style-type: none"> • Non-controversial and supported by legislation • More cells may be available per collection • Allows for future collections • Demonstrates some degree of developmental plasticity • Indicated as therapy for numerous human diseases and used in transplant for more than 40 years 	<ul style="list-style-type: none"> • Less proliferative than younger cell types • Tolerant of only 1 or fewer HLA antigen mismatches • Provides older cells with shorter telomeres • Invasive collection procedure that poses some risk to the donor • Registries are subject to donor attrition • Increased rate of GVHD compared with use of younger cells
Newborn	<ul style="list-style-type: none"> • Non-controversial, readily available, and supported by legislation • Highly proliferative, which improves the rate of self-renewal • Increased developmental plasticity, enabling differentiation into multiple cell types • Tolerant of 2 or more HLA mismatches due to immunologic naiveté • Indicated as therapy for numerous human diseases and used in transplant for more than 15 years • Decreased rates of GVHD • Young cells with longer telomeres 	<ul style="list-style-type: none"> • One-time collection, at birth only • Cell count limited to quantity available at birth, until expansion technologies are approved for use in patients • Delayed engraftment when samples with decreased cell dose are used
Embryonic	<ul style="list-style-type: none"> • Highly proliferative, which improves the rate of self-renewal • Increased developmental plasticity, enabling differentiation into multiple cell types • Involved in research that furthers our understanding of cellular development • Young cells with longer telomeres 	<ul style="list-style-type: none"> • Controversial and heavily restricted, even for research purposes • No validation in human patients • Difficult to regulate and prone to teratoma formation

than 75 conditions, including leukemia, lymphoma, hemoglobinopathies, bone marrow failure syndromes, congenital immunodeficiency syndromes, and inborn errors of metabolism.² Umbilical cord blood also contains extremely primitive circulating stem cells that, prior to birth, contribute to embryonic development. These highly plastic cells have demonstrated the potential to form bone cells, fat cells, skeletal muscle, nerve stem cells, basic mature nerve cells, and blood vessel material. It has also been shown that cord blood is a rich source of cells that share characteristics with human embryonic stem cells. These cells, termed “cord blood-derived embryonic-like cells,” have further shown the ability to form tissues from all 3 germ layers, including blood, neural, endothelial, and hepatic cells.³ Cord blood is also readily available, offers reduced risk of viral contamination, and is

easy to collect without trauma to the mother or child.

Human embryonic stem cells

have been used experimentally since 1998, and their use remains controversial and limited to research. Although their developmental plasticity provides significant therapeutic potential, researchers have not yet determined how to control their proliferation or guide their development into specific cell types. Creation of new embryonic stem cell lines is heavily restricted in the United States, which significantly limits the range of HLA antigen types available in the event that embryonic stem cells are approved for human therapy.

Conclusions

Stem cells offer significant potential for the treatment of serious diseases; however, stem cells from different sources vary in their current and future clinical utility. Clinicians and their patients need to be aware of current and developing clinical applications of stem cells and the possibilities that may affect future use of types of

stem cells as therapeutic agents. Although embryonic stem cell research is limited at this time, its future usefulness in therapy remains promising but as yet indeterminate. Both bone marrow and NBSC have strong foundations of clinical experience in the treatment of more than 75 diseases. Bone marrow has been used therapeutically for more than 40 years, and NBSC have been used for more than a decade. Given the accessibility and availability of large quantities of NBSC, it seems likely that much of the future of stem cell therapy will depend heavily on NBSC.

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Newborn stem cell transplantation: The medical literature

Over the last 2 decades, the use of newborn stem cells (NBSC) from human umbilical cord blood has become standard care for many diseases traditionally treated with bone marrow, including hematological malignancies, metabolic disorders, and autoimmune conditions. Furthermore, NBSC are easily acquired at birth and are associated with decreased incidence of serious side effects such as graft-versus-host disease (GVHD).

The results of transplants using NBSC have supported their use in transplant as a strong alternative to bone marrow stem cells. Investigations have established the following:

- Safety and efficacy of NBSC transplants
- Efficacy in pediatric and adult populations
- Impact of various doses of NBSC
- Effects of antigen mismatches on outcomes
- Favorable comparisons of NBSC with bone marrow transplant outcomes
- Utility of techniques to expand volume
- Protocols for immunosuppression

Development of NBSC banks

Family and public cord blood banks were established in the early 1990s to increase access and availability of umbilical cord blood and NBSC. Public banks maintain an inventory of cord blood samples that can be searched by the general public for HLA antigen-matched samples. Family banks were established to serve parents who would like to preserve genetically-matched NBSC for their family's exclusive use. The development of the public and family banking systems set the stage for increased use of cord blood stem cells in transplantation, research, and clinical trials. To preserve stem cells for future use, researchers established procedures for collecting, processing, and freezing cord blood units.¹² Today, at least 37 cord blood banks operate in 21 countries.³ By 2006, more than 6000 NBSC transplants had been performed worldwide (TABLE 1).^{4,6} Current practices in cryo-preservation have been shown to be effective in maintaining cell viability for at least 15 years, but if maintained at constant temperatures, preserved samples should continue to be effective.⁷

TABLE 1

Important dates in newborn stem cell transplantation

1983	Cord blood proposed as source of stem cells
1988	First newborn stem cell transplant, from a related donor, for Fanconi's anemia
1992	First family newborn stem cell bank (for use by related individual)
1993	First successful transplantation from an unrelated donor
1997	NEJM study demonstrated higher survival rates with related newborn stem cell transplants than with unrelated
2005	Congress passed the Stem Cell Therapeutic and Research Act
2006	More than 6000 transplantations have been performed worldwide

Overall, data show that when adequate doses of NBSC are administered to treat malignant and nonmalignant diseases, results are comparable to those achieved with bone marrow transplantation. However, GVHD decreases and survival increases when genetically-related NBSC are used, as compared to unrelated NBSC.⁸ Based on the strength of these data, many transplant experts advocate a routine parallel search of bone marrow and NBSC matches for unrelated donors if a related donor is not available.⁹ These results suggest that as clinical experience grows, NBSC will increasingly be used as a bone marrow equivalent.

NBSC versus bone marrow transplant

Because NBSC are immunologically less mature than adult stem cells, they can be used for transplantation with only 4 or 5 out of 6 matched HLA loci, and NBSC transplantation results in decreased rates of GVHD compared with transplants of adult stem cells.¹⁰ Cord blood contains high levels of early progenitor T cells and B cells that express

TABLE 2

Comparative studies: Newborn stem cells and bone marrow in children

	CB	BM
Engraftment	↓	↑
Acute GVHD	↓	↑
Chronic GVHD	↓	↑
Early TRM	↔	↑
Relapse	↔	
Survival	↔	

CB studies: Rocha V, et al. *Blood*. 2001;97:2962-2971; Barker JN, et al. *Blood*. 2001;97:2957-2961.

BM studies: Sharathkumar A, et al. *Bone Marrow Transplant*. 2004;33:39-45; Jacobsohn DA, et al. *Bone Marrow Transplant*. 2004;34:901-907.

“naïve” phenotypes,¹¹ and low levels of mature T cells in comparison with adult stem cells. These characteristics may explain why antigen matching can be less important with NBSC compared with adult stem cells. Furthermore, lower antigen specificity broadens the pool of available donors, increasing the chances of finding an HLA antigen match among NBSC donors compared with adult bone marrow donors. The reduced risk of GVHD may be related to the high amounts of interleukin-10 associated with cord blood.¹²

Newborn stem cells are also more proliferative than adult stem cells; cultures of NBSC increase in cell number far more rapidly than do similar cells from adult bone marrow.¹³ This could be attributed to the relatively long telomeres of cord blood stem cells.¹⁴

Various investigations have compared cord blood transplantation with bone marrow transplants, summarized in **TABLE 2**.¹⁵⁻¹⁸

NBSC transplantation in adults

The earliest clinical data regarding NBSC originated in pediatric transplants;⁵ technologies to expand cell count had not been developed and only small volumes of cord blood were available. The intervention was, therefore, believed to be most likely to succeed in young children who would require smaller dosages. However, more recent data comparing the outcomes of cord blood and bone marrow transplants indicate that NBSC transplants are also effective in adult patients.^{19,20}

In the past, the use of NBSC in adult transplants showed lower survival rates than in pediatric studies. Long-term engraftment has been well documented; efforts have focused on strategies to improve short-term engraftment including the following:

- Expansion of progenitor cells
- Transplantation using more than 1 cord blood unit
- Nonmyeloablative conditioning
- Simultaneous infusion of NBSC and highly purified progenitor cells
- Co-transplantation of NBSC and mesenchymal cells
- Expansion of progenitor cells on stromal cells
- Intraosseous transplantation

Transplants with related and unrelated donors

Like bone marrow stem cells, NBSC from related and unrelated donors have been successfully transplanted and have resulted in sustained engraftment in children and adult patients.^{5,6} Cumulatively, the data suggest that with NBSC, 2 or fewer HLA antigen mismatches significantly increase the probability of survival.²¹ This is in contrast to bone marrow, which allows no more than 1 mismatch and preferably none. Furthermore, whether bone marrow or cord blood is evaluated, stem cells from a related donor have a greater chance of HLA antigen matching. However, because cord blood requires fewer HLA antigen matches, NBSC from a related donor provides the greatest chance of HLA antigen matching.

Increasing cell dose to improve transplant outcome

Stem cell dose is a statistically significant predictor of transplant outcome.^{22,23} Unlike bone marrow, which can be harvested more than once, cord blood can be collected at only 1 point in time; therefore, cell dose is limited to what is collected at birth. Although NBSC transplants can succeed despite the potential influence of cell count, research is focused on ways to improve transplant outcome, including expanding the cell count in vitro and combining stem cells from 2 different cord blood samples. Many studies have effectively expanded NBSC in vitro, and current research focuses on determining optimal culture conditions. Additional studies have demonstrated the efficacy of double cord transplants,²⁴ but both NBSC samples must be HLA antigen

matched to the donor and to each other, which can complicate the donor selection process.

Conclusions

Newborn stem cell transplantation has advanced significantly over the past 2 decades and is established as a viable treatment option. Historically, the largest obstacles to the widespread use of NBSC has been concerns over cell dose and NBSC efficacy in adult patients. Because of this potential limitation, cord blood was regarded as an alternative to bone marrow for those without HLA antigen matched donors rather than as an equivalent stem cell source. However, more recent studies have drawn favorable comparisons between cord blood and bone marrow, supporting parallel use of both stem cell sources for transplant. The success of NBSC transplants has been enhanced through a variety of techniques, and research continues to improve the utility of cord blood stem cells in the treatment of many disease states.

As stem cell-based strategies are developed for non-hematopoietic disorders, NBSC may have an advantage over adult stem cells. NBSC have exhibited enhanced developmental plasticity, which increases the ability to differentiate into a variety of cell lines, including neurons, cardiomyocytes, islet cells, oval cells, and other tissue types. This could give NBSC an important role in the field of regenerative medicine.

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Emerging applications for newborn stem cells

Regenerative medicine has become an increasingly active area of scientific inquiry. In the past 5 years, researchers have published a wealth of data to support the regenerative potential of newborn stem cells (NBSC). Stem cells used in human regenerative medicine are primarily autologous, eliminating the risk of graft rejection. The nature of the conditions being treated with stem cells suggests that the best results are obtainable with the patient's own stem cells.

These data suggest that NBSC have the potential to differentiate into solid organ tissue-specific cells, which could provide therapeutic options for many conditions. In cultures, NBSC have expressed cellular phenotypes that include fat, bone, and neural cells and can be differentiated into muscle, myocardium, hepatocytes, and oligocytes.^{1,5} Adult and newborn stem cells are being evaluated as therapeutic options for conditions that include myocardial infarction (MI), diabetes, stroke, traumatic brain injury (TBI), and spinal cord injury. Some of the areas of investigation discussed below are currently in human trials. NBSC exhibit considerable developmental plasticity, which should make these stem cells stronger candidates for regenerative therapy than bone marrow. Furthermore, low cell dose may not be an issue in regenerative therapies.

A 2005 investigation by McGuckin et al⁶ demonstrated the potential of immature NBSC to "transform" into specific differentiated cell types. The investigators used a combination of 2-dimensional and 3-dimensional culture system technology to cultivate greater numbers of cells than was previously possible (the 3-dimensional technology was derived from the National Aeronautics and Space Administration). These advances allowed the researchers to integrate cells, build the scaffolding on which tissue grows, add nutrients, and apply mechanical forces to produce clusters of embryonic-like stem cells. The cells grew in several stages of proliferation. In this study, the cells were maintained in an undifferentiated state for 13 weeks. When stimulated with hepatic cues, they expressed hepatic-specific antigens and developed into defined liver tissue, thus demonstrating the potential of NBSC to grow into functioning tissues and organs.⁶ This technology provides methods to produce large supplies of human umbilical cord blood (HUCB) cells, which has long

been a challenge to NBSC use. Researchers are moving forward to bring this technology to clinical trials.

NBSC administration and cardiac repair

Current interventions for MI are often insufficient to prevent left ventricular remodeling and subsequent heart failure. Accordingly, myocardial regeneration or repair stimulated by the implantation of healthy cells may represent a treatment advance.^{7,8} In this extremely active area of research, clinical trials with bone marrow stem cells are ongoing. There are active clinical development programs for autologous whole bone marrow and bone marrow-derived mesenchymal stem cells (MSC). Infusion of bone marrow cells into the coronary arteries of patients following MI improves cardiac function and may reduce the size of the cardiac injury. In animals, MSC are well characterized as an agent that both improves cardiac function and reduces infarct size. Skeletal myoblasts are more controversial as a reparative cellular agent. Stem cells derived from cord blood represent a promising new source of cells for cardiac therapy.⁹

Animal studies of NBSC. A recent investigation in NOD/scid-mice following MI demonstrated that cord blood cells migrate to infarcted but not uninjured myocardium. In the infarct areas, they engraft, aid in neoangiogenesis, and beneficially influence the remodeling process.¹⁰ Research is also being conducted to understand the contribution of NBSC to vascularization.¹¹

Additional studies in large animal models substantiate the possibility that cells cultured from HUCB engraft and stimulate cardiac recovery following myocardial injury.¹² The cultured cells that proliferate from the NBSC resemble MSC cultured from bone marrow; to date, head-to-head comparisons of these 2 cells types have not been performed.

Preclinical studies of bone marrow MSC

Allogeneic bone marrow MSC injected directly into the heart via a catheter in animals produced gradual progression to normal contractility after 8 weeks. Functional recovery was accompanied by new tissue growth and a reduction in infarct size.¹²

Additionally, transplanted bone marrow cells are rich in angiogenic growth factors and are likely to induce angiogenesis and neovascularization, independent of other events. These cells may also reduce inflammation and recruitment of monocytes, stimulate endogenous progenitor cells, and release cytokines that contribute to myocardial healing and repair. They also may passively limit infarct expansion and remodeling, increase scar thickening, and reduce wall stress and motion of infarct.¹³ It is likely that NBSC may possess similar or possibly even superior properties, and may represent a readily available source of cells for myocardial cell-based therapy. Future studies are required to assess this important hypothesis.

Human trials. Several placebo-controlled, randomized studies have been conducted of autologous mononuclear bone marrow cells in patients with acute MI. The BOOST trial, the first of these studies, enrolled 60 patients following successful percutaneous coronary intervention for acute ST-segment elevation MI. The control group (n=30) received optimum postinfarction medical treatment. The other group (n=30) received optimum medical treatment and intracoronary transfer of autologous bone marrow stem cells 4 to 8 days after percutaneous coronary intervention. At 6 months follow-up, global left ventricular ejection fraction (LVEF) increased by 0.7% in the control group and 6.7% in the bone marrow cell group; the difference between the 2 groups was statistically significant. Bone marrow stem cell therapy enhanced left ventricular systolic function primarily in myocardial segments adjacent to the infarcted area. Cell transfer did not elevate risk for adverse clinical events, in-stent restenosis, or proarrhythmic effects.¹⁴

There are many ongoing studies of autologous bone marrow, and clinical programs to evaluate MSC are underway.¹⁵ In the near future, we expect to see trials using other cell types, and NBSC represent an ideal candidate.

Type 1 diabetes: NBSC administration and beta cells

Type 1 diabetes is an autoimmune-mediated disease associated with a destruction of the insulin-producing islet cells of the pancreas. Today, 1 in every 300 children will develop type 1 diabetes, and 20.6 million Americans have diabetes. Although the majority of diabetes in the United States is type 2 diabetes, the incidence of type 1 diabetes continues to increase 3% to 5% per year. According to death certificates, diabetes contributed to more than 224,000 deaths in 2002. That year, 44,400 people with diabetes began treatment for end-stage renal disease. An

estimated 12,000 to 24,000 new cases of blindness are caused by diabetic retinopathy each year.¹⁶

NBSC can potentially reduce the severity of diabetes. Several hypotheses have been suggested to explain how NBSC therapy may improve insulin production in patients with type 1 diabetes. Specifically, cord blood, rich in regulatory T cells, may help retrain the immune system and reduce islet cell destructive effector T cells. In addition, NBSC may migrate to the damaged pancreas and provide “regenerative factors” that allow for improved proliferation of normal islet cells. Finally, NBSC may migrate to the damaged pancreas and directly improve insulin production by transdifferentiating into functional islets.

Animal studies. Several studies have shown that either bone marrow or NBSC can reduce insulinitis and reverse hyperglycemia in mice with autoimmune diabetes.¹⁷ In 1 study, mice that exhibited typically autoimmune type 1 diabetes by age 12 weeks were injected retro-orbitally with various doses of NBSC, with no immunosuppression treatment, prior to onset of diabetes. Treated mice showed significantly lower blood glucose levels, reduced insulinitis (which is characterized by edema and infiltration of small numbers of white blood cells), and lengthened life span, compared with untreated mice.¹⁸

Human trials. A clinical Phase I/Phase II trial to evaluate the effect of autologous NBSC transfusion for type 1 diabetes is currently recruiting children at the University of Florida. Patients have been recruited from Florida, Michigan, California, New Jersey, and Mexico. Additional study subjects are actively being sought. Eligible children with type 1 diabetes must be at least 1 year of age and have autologous NBSC stored. The primary objective of the study is to regenerate pancreatic insulin-producing beta cells and to improve glucose control. Secondary goals include tracking the migration of transfused NBSC and studying changes in both metabolism and immune function associated with islet regeneration. To date, 8 patients have received autologous NBSC infusions. The study is approved by the FDA and supported by grants from the Juvenile Diabetes Research Foundation and the National Institutes of Health.¹⁹

Anecdotally, in the first child treated as part of the study, the NBSC therapy appeared to mediate her disease. She was 5 years old and diagnosed with diabetes 6 months prior to cord blood infusion. While most young children with type 1 diabetes experience a rapid decline in endogenous insulin production, this child continued to make significant endogenous insulin. One and a half years after her cord blood infusion, her C-peptide levels were 0.56 ng/dl; she received 0.63 units/kg/day of insulin; and her HbA1c was 6.6%.²⁰

Neurological injury and disease: Recent advances

The impact of NBSC on brain function has been under investigation for several years, and researchers have noted that cells tend to migrate to damaged areas in the brain and spinal cord. In 2001, investigators reported that NBSC progenitor cells exposed to nerve growth factor (NGF) and retinoic acid are driven toward neuronal and glial fates. Musashi I and III beta tubulin, proteins found in early neuronal development, also are expressed in NBSC, thus suggesting that NBSC could be a valuable stem cell source for cell-based therapy of brain injury and diseases. Additionally, as apoptosis occurs over a 9- to 12-month period following TBI, the use of NBSC may provide a long time frame for therapy.²

Stroke treatment

Given appropriate culture conditions, both mesenchymal stem cells and NBSC express neural phenotypes, although posttransplantation issues remain. Researchers are seeking to discover if the changes remain stable and if engraftment of functional neuroglial cells occur. Recent studies show encouraging results and provide important clues.

Animal studies. Infused newborn stem cells have been shown to produce an anti-inflammatory—and neuroprotective—effect that results from decreased expression of proinflammatory cytokines as well as decreased CD45/CD11b and CD45/B220 positive cells in the stroke hemisphere. In the rat model, investigators showed that intravenously infused NBSC enter the brain, where they survive and differentiate to improve neurological functional recovery after stroke. In one study, a 2-hour transient middle cerebral artery occlusion was performed. Functional improvement in the animals was assessed by behavioral tests (Rotarod and modified neurological severity score). In animals treated immediately with NBSC, functional recovery was improved 24 hours after the event, as verified by both test results ($P < .05$). Significant cell migration was observed 24 hours after the event ($P < .01$) compared with untreated animals. The authors noted that treatment with NBSC offer a therapeutic window of days, compared with the current 3-hour window for treatment associated with recombinant tissue plasminogen activator. In animals untreated until 7 days after the event, improvement occurred only in the modified neurological severity score ($P < .05$).²¹

Spinal cord injury

Transplantation of various cells—including Schwann cell sheaths, fetal neurons, olfactory ensheathing glia, neuronal progenitor cells, transfected cells that produce growth fac-

tors, and embryonic stem cells—have been evaluated for spinal cord injury. Studies of TBI have reported that NBSC target and migrate to areas of damage and engraft within these areas. In spinal cord injury treatment, these characteristics could eliminate the need to introduce cells directly into the central nervous system.

Animal studies. In one study, spinal cord-injured rats treated with infused NBSC were significantly improved 5 days after administration compared with similarly injured but untreated animals. Cord blood-derived cells were observed in areas of injury but not in other areas of the spinal cord. These results support the hypothesis that cord blood-derived cells migrate to and participate in the healing of neurologic defects that result from traumatic events.²²

A subsequent investigation revealed that, after spinal injury, transplanted NBSC differentiated into various neural cells, with positive effects on axonal regeneration and improved motor function.²³ NBSC were noted to be more pluripotent and genetically flexible than were bone marrow neural stem cells.

Brain injury

Animal studies. In a study of TBI, injection of human cord blood stem cells into the tail vein of rats 24 hours after injury produced behavioral improvements, as assessed through Rotarod and neurologic severity tests. The animals were assessed 28 days posttreatment and compared with controls. Subsequent testing revealed that the human stem cells preferentially migrated into the injured brain and expressed neuronal markers. The data suggest that intravenous administration of NBSC could treat TBI.²⁴ Similar benefits have been seen in hemorrhagic brain injury with bleeding in the striatum.²⁵ Beneficial effects have also been reported in perinatal brain damage and spastic paresis.²⁶

Human trials. As brain injury is the primary cause of morbidity and mortality in pediatric trauma patients, investigators are enrolling 10 children aged 5 to 14 years in a Phase I trial to determine if use of autologous bone marrow progenitor cells will benefit children with TBI. Bone marrow contains progenitor cells that are similar to those found in cord blood. The primary study goal is to assess safety; secondary objectives focus on whether late functional outcome is improved with transplantation using Glasgow outcome scores plus neuropsychiatric executive functionary tests.²⁷

These results will be compared with a very robust database of TBI developed at University of Texas Health Sciences Center at Houston over the last 15 to 20 years.

Relationship between dose and treatment

Studies demonstrate a dose relationship between NBSC infusion and subsequent behavioral improvement, along with neuronal sparing, after permanent middle cerebral artery occlusion. Trends toward improvement are also observed at lower doses. Newborn stem cells also reduce ischemic volume, especially at higher dose levels. Rats injected with NBSC 24 hours after the cerebral event had NBSC, primarily in the ischemic hemisphere, 4 weeks later. Their small numbers were primarily limited to the cerebrovasculature, suggesting that some unidentified mechanism directs them to the injured site. Other cells were seen in the spleen, implying that these cells may also modulate the immune system.²⁸

Development of the human immune system and fetal transplantation

All of transplantation medicine is dependent on understanding the biology of the immune system. The seat of human immunity is the thymus, which becomes immunologically active between 10 and 15 weeks of fetal life. The possible manipulation of fetal immunoreactivity presents a tremendous potential for prevention of many different diseases. Researchers are investigating the transplantation of NBSC into the early fetus for a prenatally diagnosed childhood or adult condition. Transplantation by fetal intraabdominal injection of NBSC is technically feasible, and could theoretically eliminate the need for chemoablation of the recipient's immune system. However, attempts to accomplish this have only been successful for fetuses with severe combined immunodeficiency syndrome. Studies of second trimester and early third trimester human fetal blood have shown heterogeneity in fetal immunity unrelated to gestational age. Flow cytometry, response to mitogens *in vitro*, and cytokine production have demonstrated this variation in fetal immunity, and shown some areas that are parallel to maternal immunity in paired samples. This suggests that NBSC immune activity will be specific for a given sample, affecting graft-versus-host disease with unrelated donors. However, we are able to diagnose disease by chorionic villus sampling at 10 to 12 weeks of gestation. It is therefore possible to transplant appropriately HLA antigen matched NBSC early in pregnancy before thymic maturation and either introduce a set of cells without the disease, or tolerate the fetus to permit successful transplantation after birth.^{29,30}

Cord blood stem cells: Emerging applications

Diseases of the ocular surface. When the tissue-specific stem cell layer of the cornea's epithelium is deficient, conjunctival growth over the corneal epithelium occurs, resulting in a

white cloudy surface and vision loss. In the rabbit model, cultured NBSC were grown on the amniotic membrane, which was transplanted. The cells differentiated to reconstitute the cornea *in vitro*, forming an optically clear surface.³¹

Liver injury repair. The hepatic oval cells express surface antigens that are similar to those of circulating hematopoietic progenitor cells. In a chemically induced animal model of hepatic injury, injection of NBSC led to development of hepatocytes, improved regeneration of damaged liver tissue, and reduced mortality.³² A 2006 investigation has shown that NBSC—in *vitro* or *in vivo*—can be differentiated into hepatocytes in the rat model.³³

Delay of symptoms of Parkinson's disease. Mice with Parkinson's disease were injected with NBSC without immunosuppression. Compared with animals receiving bone marrow cells or no treatment, those that received NBSC transplants showed significantly delayed onset of symptoms and death.³⁴

Effect on Alzheimer's disease progression. Investigators injected NBSC into transgenic mice that had an overexpression of human Alzheimer amyloid precursor proteins. Untreated, these mice die early and develop a central nervous system disorder that includes neophobia. The mice injected with NBSC survived significantly longer than did the control mice.³⁵

Increased life span in Huntington's disease. Injection of NBSC in transgenic mice with Huntington's disease increased their life spans; the rate of weight loss that precedes symptom onset was significantly reduced in comparison with controls.³⁶

Delayed onset of amyotrophic lateral sclerosis. Infusion of NBSC has modestly prolonged the life span and delayed the onset of disease in SOD1 mutant mice, possibly as a result of immune-modulating and anti-inflammatory effects.³⁷

Conclusions

Newborn stem cells are currently used to treat more than 75 diseases, and future indications continue to emerge. Animal studies and, increasingly, human trials have assessed the effects of NBSC therapy on a variety of injuries and disease states. These investigations suggest that NBSC use will expand: In 2005, the likelihood of needing an NBSC transplant was reported at 1:200, based on current indications.³⁸ However, autologous stem cells have shown clinical efficacy in the treatment of cardiovascular disease, the leading cause of death in the United States, and promising results in stroke, diabetes, and many malignancies. These conditions are among the most common causes of death in the United States. As NBSC become a treatment option for increasingly common diseases, the odds of needing an NBSC transplant

will rise accordingly. As NBSC use expands in regenerative medicine for possible joint, tissue, and organ replacement, it will likely be important to have access to immunologically-matched donor cells or autologous NBSC. Widespread clinical use of stem cell-based therapy will create a new era in medicine.

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Practical issues for clinicians: Cord blood collection and patient counseling

We need to understand what current applications and emerging research mean to our practices and our patients. Surveys have shown that patients have inadequate knowledge and understanding of umbilical cord blood banking. They may think that stem cells come only from embryos and that cloning and stem cell therapy are identical processes. Therefore they are probably unaware of recent research in cord blood stem cell transplants and private or public stem cell banking options.

Patient awareness of NBSC storage and use

In 2004, 425 women were questioned about newborn stem cell (NBSC) banking at the time of visits for obstetrical ultrasound, perinatal consultation, or ongoing obstetrical care. Ethnic minorities were found to be less likely to be aware of the possibilities for banking NBSC than were Caucasians. Overall, only 14% of patients surveyed had been educated by their health care providers; most patients who were aware of NBSC preferred that their clinician educate them on this topic.¹

Health care providers should discuss family banking and public donation with expectant parents. This is particularly important in light of recent legislation requiring that all families and pregnant women be given the choice of not banking, donating to a public bank, or storing in a private bank.² Prior to the passage of this legislation, a 1997 American College of Obstetricians and Gynecologists (ACOG) committee opinion and, subsequently, a 1999 American Academy of Pediatricians (AAP) position paper were the only sources of guidance for counseling patients about cord banking.^{3,4}

This publication is intended to assist obstetric caregivers with NBSC education. It provides information that should be considered by ACOG and AAP in making their updated recommendations.

Family versus public banks: Differences that affect decisions

Family banks. Family banks process and store NBSC for the newborn or other family members. Family banking provides immediate access to genetically-related stem cells, which

increases the chance of HLA antigen matching compared with public registries. As a community service, some family banks provide processing and storage at a nominal cost if a family member is diagnosed with a condition treatable with stem cells. Thus, in the case of an urgent medical condition, there is no need to search for donors (unless the unit does not have a match with the family member who needs it), and wait time for transplant is reduced.⁵ Family cord blood banks charge an initial processing fee that ranges from \$1100 to \$1750, followed by a yearly storage fee of \$115 to \$125. If the unit is needed, processing and shipping fees are billed to the insurance company.⁶ Some private banks may offer free storage for women or their families who have risk factors that indicate a likely need for future transplantation or for newborns with low Apgar scores or other risk factors.

Public banks. Women who elect not to store their newborn's stem cells in a family bank may be eligible to donate cord blood to a public bank. Once donated, the blood is not always available to either the baby or its family. As with blood banks and bone marrow banks, the cord blood units are made available to the public. Since 2004, a key focus of public donor banks has been to increase the size and ethnic diversity of the available cord blood pool and the creation of a computerized, Web-based system that allows users to search for donor matches.⁷ Initial processing cost is typically \$1000 per unit stored. Fees to retrieve the sample range from \$15,000 to \$35,000 per unit.⁶

Although public banks are designed to improve donor matches for minorities, a recent study revealed that cord blood donation from minorities has remained low. An American Red Cross survey showed that 64% of donors are white, 16% African American, 12% Hispanic, 4% Asian, 1% Native American, and 3% other.⁸

Making appropriate decisions

As part of the decision-making process, clinicians should review with patients the issues of NBSC transplants and those of bone marrow transplants, along with individual and family risks. The discussion should be placed within the context of prenatal counseling and consent, using detailed documentation to evaluate the options and opportunities.

A once-in-a-lifetime opportunity

One opportunity exists to collect a baby's cord blood. At an increasing rate, expectant parents are opting to collect the cord blood of their child at birth, not only to make NBSC available to their family for possible life-saving treatment of over 75 diseases, abnormalities, and injuries, but also for their emerging potential. Some families have defined risk factors, but most often, parents family bank because of the therapeutic options that stem cells may someday offer their children, themselves, or other family members.

Recent clinical studies support the unique suitability of NBSC for a number of developing technologies. Clinicians are especially enthusiastic about the potential use of cord blood stem cells in the emerging fields of gene therapy and cellular repair.

Some unique considerations for collecting and storing a baby's NBSC include:

Family health history. Newborn stem cell banking is a prudent choice if a family member has a disease that is treatable with stem cells or if there is a family history of a disease treatable with stem cells. Certainly, the causes of many diseases are unknown, and even genetically-linked diseases may occur without a family history.

Ethnic or mixed ethnicity. Ethnic minorities and families of mixed ethnicity have greater difficulty finding unrelated HLA antigen matched stem cell donors when needed. Many genetic diseases such as sickle cell anemia and thalassemia are more common in certain ethnic populations. Both of these diseases have been successfully treated with NBSC.

Newborn adoption. Families preparing to adopt a newborn may choose NBSC banking because, if ever needed, the cord blood may be the only available source of genetically-matched stem cells for the adopted baby. In addition, depending upon the terms of the adoption, complete family medical histories are not always available.

In vitro pregnancies. Couples using fertility treatments often bank NBSC because they face the possibility of not having

another opportunity to secure a genetically related sample for their child.

Conclusions

Cord blood, long considered a waste product, offers considerable therapeutic utility. Patients who are pregnant or contemplating pregnancy need to be aware of the options to ensure that they are able to make informed decisions concerning collection and storage of their newborn's cord blood. As advances in transplant technology and regenerative medicine continue, the utility of NBSC in the treatment of severe and chronic illness likely will increase. Obstetric and pediatric caregivers must be able to share their knowledge of stem cell-based medicine and NBSC banking with their patients. Prenatal counseling and preparation are essential, including consent for collection and a waiver that is obtained before the onset of labor in case the sample is not collectible. Every pregnant woman deserves to know about NBSC banking today to empower her to make decisions for tomorrow.

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