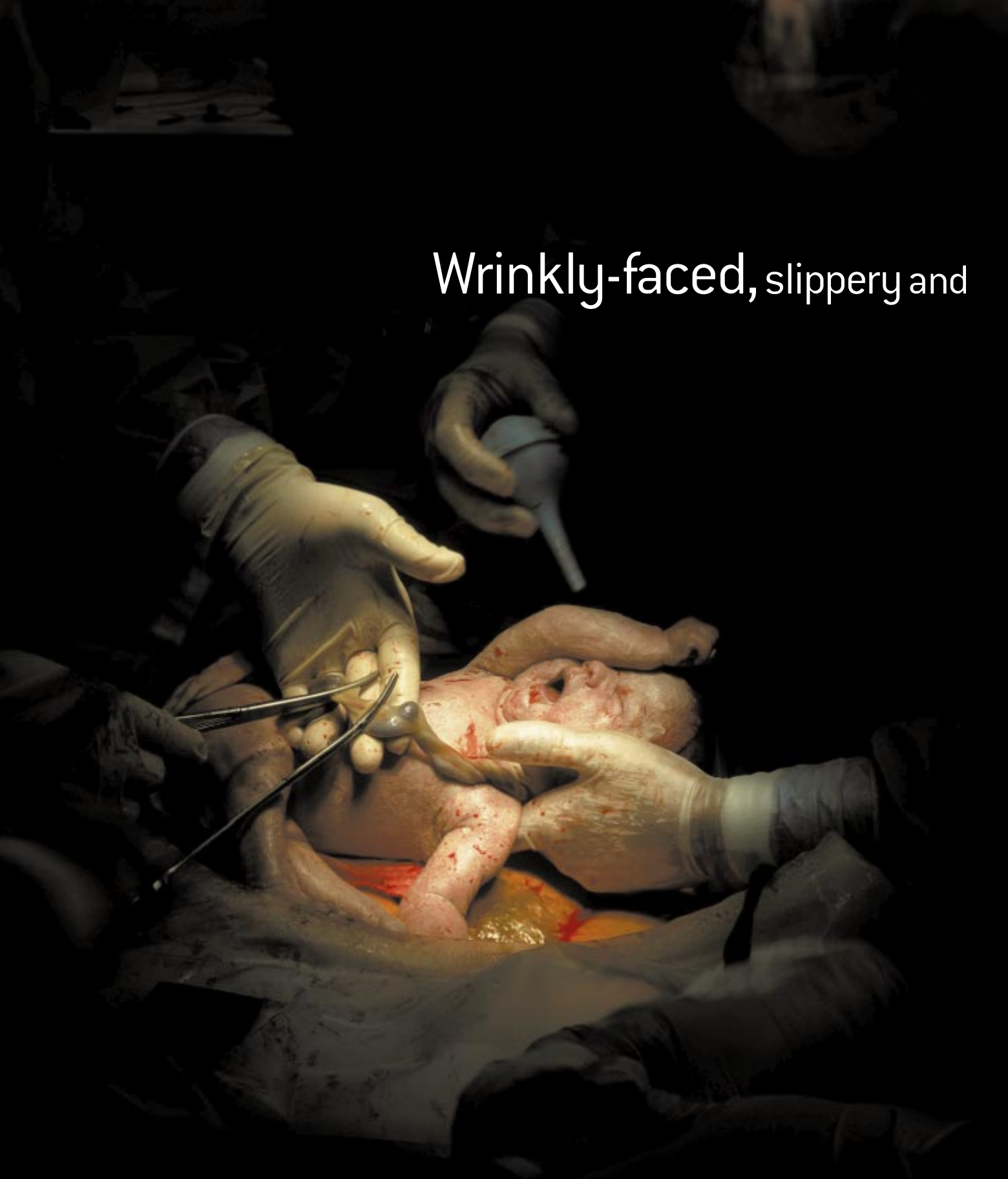
WHOSE BLOOD IS IT, ANYWAY?

Blood collected from umbilical cords and placentas—which are usually thrown away following birth—contains stem cells that can rebuild the blood and immune systems of people with leukemia and other cancers

By Ronald M. Kline >> Photographs by Max Aguilera-Hellweg

Kristina Romero, four months pregnant, plans to use the cord blood for her son with leukemia, Chase.

Wrinkly-faced, slippery and



Doctors clamp the umbilical cord of a child being delivered by cesarean section.

squalling, the newborn makes her debut into the world. As the parents share their joy and begin to count 10 perfect little fingers and 10 adorable tiny toes, they scarcely pay attention to birth's Act Two: the delivery of the placenta, or afterbirth.

After the ordeal of labor, most new mothers are happy they need to push only once more for their physician to scoop up the roughly one-pound, pancakelike organ that nourished their baby through the umbilical cord for nine months. After cutting the cord and checking the afterbirth for gaps and tears that might indicate that a piece still remains inside the mother's uterus—where it could cause a potentially fatal infection—the doctor usually tosses it into a stainless-steel bucket with the rest of the medical waste bound for incineration.

But more and more physicians and parents are realizing the value of what they used to regard as merely birth's byproduct. Since 1988 hundreds of lives have been saved by the three ounces of blood contained in a typical placenta and umbilical cord. That blood is now known to be a rich source of so-called hematopoietic stem cells, the precursors of everything in the blood from infection-fighting white blood cells to the red blood cells that carry oxygen to the platelets that facilitate blood clotting after an injury.

The stem cells from a single placenta are sufficient to rebuild the blood and immune system of a child with leukemia, whose own white blood cells are abnormally dividing and must be killed by chemotherapy. In the past, physicians had to seek a living donor to provide such children with transplants of bone marrow, which also contains stem cells that produce blood and immune cells. Unfortunately, many people have died during the long search for a donor with a matching tissue type or from complications if the donated marrow did not match well. Cord blood, which can be stored, is more likely to provide a suitable match and less likely to cause complications, because its stem cells are immunologically different from and more tolerant than those in adult bone marrow.

The benefits of umbilical cord blood transplantation have been demonstrated most conclusively in leukemia, but the process has other uses. The stem cells in cord blood can help to restore normal red blood cells in people with sickle cell anemia and to reconstitute the immune system of infants born with severe combined immunodeficiency. Cord blood can also be used to treat fatal inherited enzyme deficiencies, such as Hurler's syndrome, which results in progressive neurological degeneration and death. In such cases, the stem cells in cord blood can give rise not only to normal red and white blood cells but also to supporting cells in the brain called microglia that can provide the crucial missing enzyme there.

Recognizing the apparent advantages of umbilical cord blood transplantation, a number of medical centers have established banks so that a mother can donate her baby's cord blood for use by a stranger in need. The New York Blood Center's Placental Blood Program, pioneered by Pablo Rubinstein, now has 13,000 banked donations and is the nation's largest public cord blood bank. The University of California at Los Angeles and Duke University also have umbilical cord blood storage programs, which are federally funded.

But like many new scientific discoveries, umbilical cord blood transplantation brings with it a set of ethical questions [*see box on next page*]. Who owns umbilical cord blood: both parents, the mother or the infant? What happens if a mother donates her baby's cord blood to a bank but the child later develops leukemia and needs it? The ethical questions are compounded by the advent of for-profit companies that collect and preserve a newborn's cord blood for possible use by the family later. Is it right for such companies to aggressively market their services—which can cost $1,500 for collection and $95 per year for storage—when the chance a child will ever need his or her cord blood ranges from 1 in 10,000 (according to the New York Blood Center) to 1 in 200,000 (according to the National Institutes of Health)?

Founts of Stem Cells

THE FIRST HINT that umbilical cord blood could be clinically useful came in 1972, when Norman Ende of the University of Medicine and Dentistry of New Jersey and his brother, Milton, a physician in Petersburg, Va., reported giving a 16-year-old leukemia patient an infusion of cord blood. Weeks later the scientists found that the patient's blood contained red cells that they could identify as hav-

PHOTOGRAPH BY MAX-AGUILERA-HELLWEG *TIMEPIX*

But Is It Ethical?

Marketing tactics and privacy issues raise eyebrows

LAST SEPTEMBER a little girl from California named Molly received a lifesaving transplant of umbilical cord blood from her newborn brother, Adam. Molly, who was then eight years old, suffered from a potentially fatal genetic blood disorder known as Fanconi anemia. But what made the procedure particularly unusual was that Adam might not have been born had his sister not been sick. He was conceived through in vitro fertilization, and physicians specifically selected his embryo from a group of others for implantation into his mother's womb after tests showed that he would not have the disease and that he would be the best tissue match for Molly.

Was this ethically appropriate? A panel of bioethicists decided that it was, because donating cord blood would have no effect on Adam's health.

Selectively conceiving a potential donor is only one of the myriad ethical issues surrounding umbilical cord blood transplantation. One of the most significant has to do not with how the blood is used but with the marketing campaigns aimed at prospective parents by for-profit companies that offer to collect and store a baby's cord blood—for a hefty fee—in case he or she might need it later.

Such companies market cord blood collection as "biological insurance" to expectant parents. But "the odds are so extraordinarily against their child's ever needing it," says Paul Root Wolpe, a fellow at the University of Pennsylvania Health System Center for Bioethics. He fears that parents who can scarcely afford the service might feel impelled to buy it even though their families have no history of blood disorders.

Viacord, a cord blood–preserving company based in Boston, says that just five of their 6,500 clients have so far needed infusions of their stored cord blood. Moreover, only 20 percent have a family history of a blood disorder or are now in treatment.

The American Academy of Pediatrics issued a policy statement on umbilical cord blood banking in July 1999 cautioning that "it is difficult to recommend that parents store their children's cord blood for future use" unless a family member has had a blood disorder. Instead it encouraged parents to donate their baby's cord blood to public banks.

Questions have been raised in the past concerning the ownership of cord blood. But bioethicist Jeremy Sugarman of Duke University states that it is now fairly clear that although an infant owns his or her own cord blood, parents have legal guardianship over it—just as they do over the child—until he or she reaches age 18. Sugarman and Wolpe contributed to a 1997 consensus statement on the ethics of umbilical cord blood banking in the *Journal of the American Medical Association*.

Sugarman adds that it is perfectly appropriate for a parent to use one sibling's cord blood to treat another. If the first child develops a need for a transplantation later on, the fact that the parents already used his or her stored blood is unfortunate but not unethical.

Of more concern is how to ensure the safety of cord blood donated to cord banks. What happens if parents donate a newborn's cord blood to a public bank and the child develops leukemia years later? If the donated blood has no identifying information to link it to the donor, there would be no way to prevent it from being used in another child. Stem cells in the umbilical cord blood of a child who later gets leukemia could also cause leukemia in a recipient. But keeping permanent records of donors carries privacy risks: What if the blood is transplanted into a recipient but doesn't take, and the sick child's parents want to track down the donor child for bone marrow cells?

Most public cord blood banks label samples so they can be linked to a particular donor for several years, at which time they destroy the identifying information. Wolpe says that this is a good trade-off but that risks will always be associated with donor cord blood, just as they are with donor adult blood. "You try to keep it as safe as you can," he says, "but people take a chance."

— Carol Ezzell, staff writer

ing sprung from the donor's stem cells.

But it took years for other physicians to recognize the potential of umbilical cord blood transplantation. In 1989 Hal E. Broxmeyer of the Indiana University School of Medicine, Edward A. Boyse of Memorial Sloan-Kettering Cancer Center in New York City and their colleagues revived interest in the technique by showing that human cord blood contains as many stem cells as bone marrow does. That same year Broxmeyer, Eliane Gluckman of Saint-Louis Hospital in Paris and their co-workers reported curing Fanconi anemia—a potentially fatal genetic disorder—in a five-year-old boy using blood from his baby sister's umbilical cord. Since then, approximately 75 percent of umbilical cord blood transplants have used cord blood from a nonrelative obtained from cord blood storage programs.

What's Bred in the Bone

UMBILICAL CORD BLOOD transplantation aims to obtain a source of stem cells that is the best possible match for a particular patient's tissue type. Tissue type is determined by a set of genes that make proteins called human leukocyte antigens (HLAs), which are found on the surfaces of all body cells. The immune system recognizes cells bearing the HLA proteins it has encountered since birth as normal, or belonging to the "self." Any other HLA proteins are regarded as "nonself," or foreign; cells carrying them are quickly killed.

There are six major HLA genes. Every person has two copies, or alleles, of each—one from each parent. (Each allele can come in more than 30 different types.) For bone marrow transplants, physicians aim to match the six alleles (of the total 12) that are most clinically relevant in transplantation. But because cord blood cells are immunologically different from bone marrow cells, doctors can use donor cord blood samples that match five—or even three—HLA alleles.

The genetic blueprints for making HLA proteins are found on chromosome 6. The rules of genetics dictate that the probability that two siblings will inherit the same maternal and paternal chromosome 6—and will therefore be good tissue-type matches—is only 25 percent.

Receiving a bone marrow transplant from someone who is not a good tissue-type match is potentially fatal. On one hand, the graft can fail if even a tiny amount of the recipient's own immune cells survive to generate an immune response that deems the transplanted cells foreign and kills them. This graft failure essentially leaves the patient without a functioning immune system and extremely vulnerable to infection. Conversely, the transplanted cells can attack the recipient's body as foreign in a dire phenomenon called graft-versus-host disease. Graft-versus-host disease can manifest itself as a blistering and ulcerating skin rash, liver damage that progresses to liver failure or severe gastrointestinal bleeding; it can quickly lead to death.

To minimize such serious complications in people who cannot obtain a bone marrow transplant from a well-matched sibling, in 1987 a coalition of national blood bank organizations persuaded the U.S. federal government to establish the National Marrow Donor Program to find the best matches for patients among a pool of registered potential bone marrow donors. The program—together with other, similar, international registries—lists 6.5 million names. But because there is only a 1 in 400 chance that an individual will be a match for someone who is not a relative, those in need typically have just a 60 percent chance of finding a potentially lifesaving donor. The odds are even worse for patients who are members of a minority group, because matches are more likely to occur between people of the same race and the registries do not have enough minority volunteers.

Even those who do find a suitable donor from one of the registries still face an alarming 80 percent risk of moderate to severe (grade II to IV) graft-versus-host disease. Scientists think this is because the matching process does not consider the many unknown minor HLA proteins. Although these proteins are not actively matched in sibling transplants either, the close genetic relationship of siblings ensures that many of them will be matched simply by chance. A good sibling pairing, however, still carries a 20 percent risk of graft-versus-host disease.

One way to slash this incidence would be to attempt to match all known HLA proteins, but that would drastically reduce the chances of finding any potential donor for a recipient. Umbilical cord blood transplantation offers a better alternative. Because of differences in the newborn's immune system, immune cells in umbilical cord blood are much less likely than those in an older child's or an adult's bone mar-

For-profit companies will preserve a newborn's cord blood for possible use by the family later. Is that right when the chance a child will ever need his or her cord blood ranges from 1 in 10,000 to 1 in 200,000?

A placenta and umbilical cord ready for cord blood collection.

THE AUTHOR

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row to attack a recipient's tissues as foreign and cause graft-versus-host disease.

In 1997 Gluckman and her colleagues found evidence that umbilical cord blood transplantation—even between an unrelated donor and recipient—is safer than bone marrow transplantation. Her group studied 143 patients who had received umbilical cord blood transplants either from relatives or from a donor program. Although the transplants ranged from fully matched to two-thirds mismatched, the incidence of life-threatening (grade III or IV) graft-versus-host disease was just 5 percent in the related group and 20 percent in the unrelated group. It caused the death of only 1 percent of the related group and 6 percent of the unrelated group. In comparison, large studies using fully matched, unrelated bone marrow donors have shown a 47 percent incidence of life-threatening graft-versus-host disease, with 70 percent of those patients (33 percent of the total) eventually dying from the disease.

Umbilical cord blood transplantation has many other potential advantages over standard bone marrow transplants. The size of the potential donor pool is much larger for cord blood than for bone marrow, for example. The National Marrow Donor Program has required more than a decade to accumulate a pool of four million individuals who have been typed for potential bone marrow donation (the other 2.5 million donors are registered in other countries). But there are four million births in the U.S. annually, each of which is a potential opportunity to collect cord blood. The New York Blood Center has been able to provide suitable donors for 85 percent of its requests using a pool of only 13,000 stored cord blood samples. The pool represents just over a single day's births in the U.S.

Cord blood also has advantages in speed. Identifying a suitable unrelated bone marrow donor is a time-consuming process that takes an average of four months. During this period, potential donors are asked to go to donor centers to have blood drawn for tissue typing and testing for viruses such as the ones that cause AIDS and hepatitis. After a donor is selected, that individual must return, pass a physical examination, give his or her informed consent and then schedule a time for the bone marrow to be harvested from the hipbone using a needle.

In contrast, cord blood is readily available from a bank's freezer and has already undergone viral testing and tissue typing. An umbilical cord blood match can be

One day an infant born with a **genetic defect** of the bone marrow or blood may be able to have his or her umbilical **cord blood** harvested at birth, repaired by genetic engineering and then reinfused.

A sample of frozen cord blood banked at the New York Blood Center.

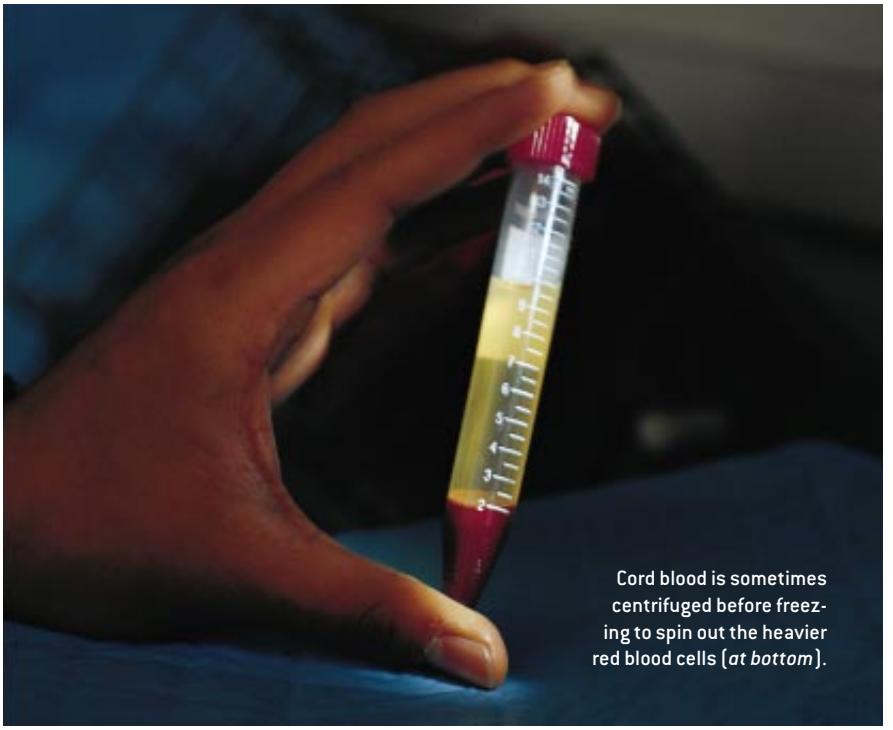
made in as few as three or four days, which can spell life or death for someone who is already immunodeficient and at high risk for a fatal infection. The collection of umbilical cord blood from as many donors as possible would also increase the likelihood that people from minority groups would be able to find a match. According to the National Marrow Donor Program, African-Americans have only a 57 percent chance of finding a bone marrow donor. Pacific Islanders and Asians have a higher match rate of 74 percent; Hispanics have a 78 percent chance; and American Indians and Alaska Natives have an 84 percent likelihood of finding a donor. Caucasians have odds of 87 percent.

Cord blood will also be virtually free of a virus that in the past has been responsible for 10 percent of deaths following bone marrow transplants: cytomegalovirus (CMV). More than half of the adult U.S. population carries CMV, which continues to live in the white blood cells of the host after initial infection. Although CMV generally causes an innocuous viral syndrome in a healthy person, it can kill someone who is immunosuppressed after a bone marrow transplant. Bone marrow donors are tested for CMV, but patients often receive CMV-positive marrow if it is the best match. Because fewer than 1 percent of infants contract CMV in the womb, umbilical cord blood could be much safer than bone marrow.

The Downside

CORD BLOOD TRANSPLANTATION is not without risks, however. One is the chance that the stem cells in a cord blood sample might harbor genetic mistakes that could cause disease in a recipient. Such disorders—which could include congenital anemias or immunodeficiencies—might not become apparent in the donor for months or years, by which time the cord blood might have already been transplanted into another recipient.

Umbilical cord blood banks could largely avoid this risk by quarantining the blood for six to 12 months and by contacting the family at that time to ensure that the donor is healthy. A long-term identification link between a donor and his or her unit of cord blood would be necessary, a prospect that has aroused privacy concerns among medical ethicists.



Cord blood is sometimes centrifuged before freezing to spin out the heavier red blood cells (*at bottom*).

Currently the New York Blood Center asks potential donor parents to complete detailed questionnaires that emphasize their family histories of disease as well as their sexual histories. If responses to the questionnaire generate medical reservations, the center does not collect or store the cord blood. The center maintains only a short-term link with the donor until viral testing is complete, when the cord blood becomes anonymous.

Another limitation of umbilical cord blood is the relatively small number of stem cells contained within a single sample. Although cord blood can be used for transplantation in adults, studies by Pablo Rubinstein have demonstrated that because of the limited number of stem cells in cord blood, larger (that is, older) patients benefit less than smaller (younger) patients. Researchers are now working to devise ways to increase the number of stem cells in cord blood samples using nutrients and growth factors. They are also genetically engineering stem cells to correct genetic disorders such as severe combined immunodeficiency. In such a case, physicians would collect a patient's own cord blood, insert normal genes into the stem cells of the cord blood and reinfuse the cells into the child's body.

All of this portends even more exciting uses for cord blood. One day an infant born with a genetic defect of the bone marrow or blood may be able to have his umbilical cord blood harvested at birth, repaired by genetic engineering and then reinfused, so that he need never suffer the negative effects of his genetic inheritance. Alternatively, such a child could be cured by the infusion of stem cells from an unrelated—but perfectly matched—sample of umbilical cord blood from a donor bank. These scenarios will soon move from the realm of science fiction to science, as advances in biotechnology expand the potential of umbilical cord blood to cure diseases that once were fatal. SA

MORE TO EXPLORE

Ethical Issues in Umbilical Cord Blood Banking. J. Sugarman, V. Kaalund, E. Kodish, M. F. Marshall, E. G. Reisner, B. S. Wilfond and P. R. Wolpe in *Journal of the American Medical Association,* Vol. 278, No. 11, pages 938–943; September 17, 1997.

Umbilical Cord Blood Transplantation: Providing a Donor for Everyone Needing a Bone Marrow Transplant? Ronald M. Kline and Salvatore J. Bertolone in *Southern Medical Journal,* Vol. 91, No. 9, pages 821–828; September 1998.

For more details on the cord blood transplantation process, visit the University of California at Los Angeles site at **www.cordblood.med.ucla.edu**