Clinical Promise, Ethical Quandary

The burgeoning interest in transplanting umbilical cord blood as an alternative to bone marrow to treat a variety of life-threatening diseases is raising questions about genetic testing and informed consent

For lethal diseases such as severe leukemia and inherited immune deficiencies, bone marrow transplantation is often a lifesaver. But bone marrow is hard to come by, expensive, and, all too often, the cause of severe immunologic reactions that can be as deadly as the underlying disease. Recently, however, researchers have been reporting success with transplantations of material that is abundant, cheap, and well tolerated: blood from the umbilical cord.

Once discarded as medical waste, cord blood has become a hot clinical property in the past 3 years. Physicians in the United States and Europe have now used cord blood in scores of operations to restore bone marrow in patients whose own marrow has been wiped out by disease or cancer therapy (*Science*, 12 May 1995, p. 805). Its value lies in the "stem cells" it contains. Similar to those in bone marrow, these cells are progenitors of the body's many types of peripheral blood cells. Early results suggest that cord blood is a safe and effective transplant material that can be used to treat patients who are not related or even well matched immunologically to the donor—and with fewer complications than with bone marrow. "It's working: Despite mismatches, it enables engraftment and long-term survival of patients," says oncologist Joanne Kurtzberg of Duke University Medical School, who has done more cord blood transplants than any other physician. John Wagner of the University of Minnesota (UM), another leader in the field, is enthusiastic, too. "It's going extraordinarily well," he says.

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Transplant pioneer. Joanne Kurtzberg has done more cord blood transplants than any other physician.

But as the boom takes off, accompanied by a surge of media publicity, it brings with it an "incredibly complicated" set of ethical and clinical dilemmas, says Kurtzberg. How should cord blood be collected and stored? Do you need to obtain consent from the donor's parents or guardians to conduct a battery of tests on the material? How do you protect their privacy? Who owns the blood? If it's tested for genetic diseases, do you tell the donor the results? And how do you regulate companies that are selling parents on the idea that they should bank their own children's blood as "insurance" against future needs, although the chances that those needs will ever arise are remote? Responding to worries about this last question—a topic that is growing increasingly contentious—the U.S. Food and Drug Administration (FDA) recently announced that it is moving into the field as a regulator (see box).

Transplant surgeons welcome the FDA's move. But it's not just commercial outfits that need watching, says Wagner: "Many centers that are not-for-profit are also considering cord blood banks. We want to make sure that when we offer this to a patient, it's coming from a reputable place." And physicians would like FDA to tackle the many ethical issues that need sorting out. Yet they also have reservations about the government taking an active role. Kurtzberg, for example, favors developing ethical guidelines, but she hopes "we can work them out as we're banking," rather than hold out for a consensus. If banking must wait until final rules are in place, she warns, "I think that we will never be able to begin banking," delaying wider use of the technique.

Good and plenty

Although skeptics point out that very little data have been published as yet (Kurtzberg's work is in review), the enthusiasm about cord blood is spreading. About 200 cord blood transplantations have been conducted worldwide since 1988. Pablo Rubinstein, research director of the New York Blood Center—which has supplied cord blood for more than half the transplants (106) to date—says "it's not a panacea," but "the results [of the early transplants] have been good."

And the technique recently won a vote of confidence from the National Heart, Lung, and Blood Institute (NHLBI): According to NHLBI official Paul McCurdy, the government plans to invest about $24 million in contracts over the next 5 years, starting this spring, to support a network of cord blood banks and experimental transplant centers. NHLBI is already supporting Rubinstein's efforts with a grant of $4.5 million in 1992 to set up a pilot project; the center now holds the world's largest cord blood reserve (5000 units of 82 ml on average).

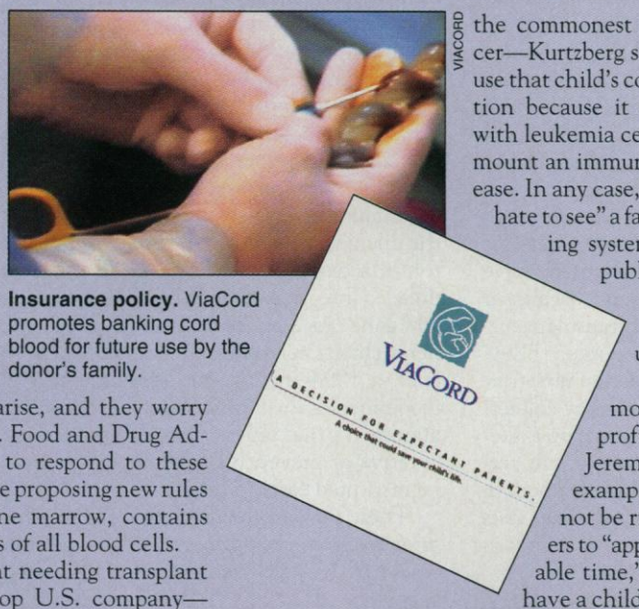
Donald Kohn at the Children's Hospital of Los Angeles and other researchers also believe that cord blood may be an excellent medium for gene therapy. The idea is that if early-stage stem cells in cord blood can be coaxed to take up a modified gene, they are likely to live longer than peripheral blood cells and give rise to a large progeny of genetically modified daughter cells.

The pioneers of this field—like Hal Broxmeyer of the Indiana University School of Medicine, who took part in the first cord blood transplant in 1988—say this growing enthusiasm stems from the fact that cord blood has several advantages over bone marrow. For one thing, it's more widely available. The National Marrow Donor Program has more than 2 million volunteers in its data banks, but it provides matched donors for less than one third of the patients needing donations. Even after a match is found in the registry, Broxmeyer says, "you have to go track down that person" and persuade him or her to undergo an operation in which marrow is extracted. As a result, after finding a match, 3 to 6 months can elapse before transplantation. Wagner notes that "many patients die while waiting for a donor, or develop an infection and become a higher risk patient." Experience has shown, says Jeffrey McCullough, a founder of the bone marrow donor program at UM, that about 25% of the donors in the registry cannot or will not undergo the unpleasant donation procedure. With banked cord blood, the donation has already taken place.

Cord blood's clinical value rests in its rich content of stem cells and the fact that it appears to provoke a less severe immune response from the recipient. Wagner points out that in bone marrow transplants, even when donors and recipients are immunologically matched, the risk of developing a severe or lethal immune reaction—grade 3 or 4 graft versus host disease (GVHD)—is 40%. But in his experience with 14 cord blood

Private Cord Blood Banks Raise Concern

Pablo Rubinstein, keeper of the world's largest repository of blood from umbilical cords, is amazed by the boom in his field. "Every time I look around," says Rubinstein, who is research chief at the New York Blood Center, "I keep finding more people who want to start a cord blood bank." Rubinstein has heard of "about six" companies that want to create new, for-profit storage centers. This rush to commercialize what he regards as a public resource worries Rubinstein and many others in the field. They are concerned that parents are being encouraged to bank their children's blood for needs that are unlikely ever to arise, and they worry about the absence of regulations. The U.S. Food and Drug Administration (FDA) has, however, begun to respond to these concerns. In December, FDA said it would be proposing new rules on the use of cord blood, which, like bone marrow, contains critical "stem cells" that are the progenitors of all blood cells.



Insurance policy. ViaCord promotes banking cord blood for future use by the donor's family.

Rather than offering help to any patient needing transplant material, private outfits offer what the top U.S. company—ViaCord Inc. of Boston—calls a form of "insurance" for families that can afford it. For a one-time fee of $1500 plus an annual charge of $95, ViaCord will collect a newborn's cord blood and preserve it in liquid nitrogen. The idea is to guarantee the child and family members a compatible substitute for bone marrow.

"It's sort of like amniocentesis," says Cynthia Fisher, ViaCord's president. "Not everybody does it, but it's a choice people can have." She anticipates great demand for this "priceless" material, saying, "We have heard that stem cell therapy [based on derivatives of cord blood] would be useful in treating a variety of cancers like leukemia, a variety of genetic blood disorders such as Fanconi's anemia, thalassemia, and Gaucher's disease." She even foresees "hope in the area of sickle cell anemia" and solid tumor therapy.

Many clinicians, even among gung-ho advocates of using cord blood as a substitute for bone marrow, are disturbed by this optimistic pitch. Pediatric transplanter Joanne Kurtzberg of Duke University Medical School says the likelihood that a normal child would need his or her own stem cells later in life is "very small." For example, even if the child were to develop leukemia—the commonest form of childhood cancer—Kurtzberg says she wouldn't want to use that child's cord blood for transplantation because it might be contaminated with leukemia cells or might be unable to mount an immune attack against the disease. In any case, Kurtzberg adds, "I would hate to see" a family-based private banking system "take away from" the public banks, because the "great need" will be for blood transfers between unrelated people.

Some people are even more critical of the for-profit banks. Medical ethicist Jeremy Sugarman of Duke, for example, says he thinks it may not be right for cord blood bankers to "approach parents at a vulnerable time," just as they're about to have a child, and charge for a service the majority will never use. Michael Grodin, director of medical ethics at Boston University, is harsher: He says selling cord blood services is "outrageous," "wrong," and a form of "exploitation."

But ViaCord's Fisher, while agreeing that the odds of people using their own stored cord blood are "small," says parents are fully informed of the speculative nature of their investment. She adds that "we, as a company, see it as a potential lifesaving material, and we are giving families a new chance they never had before: Why not save it?"

In mid-December the FDA released a draft statement that it intends to regulate cord blood at least as stringently as standard blood. FDA's Liana Harvath says the agency received many calls last year urging action. The result: FDA has declared that cord blood will be controlled as a "biologic." Anyone offering the material for therapy will need to obtain an Investigational New Drug application from FDA. This will enforce minimal standards and raise new financial barriers to entering the field—and, FDA officials say, focus public scrutiny on it.

–E.M.

transplants, "we have never seen grade 3 or 4 GVHD," and the overall GVHD rate is 1.6%. "We don't have a randomized trial to prove it ... but that's low," Wagner says. The success that Wagner and Kurtzberg are seeing is even more remarkable because each has carried out cord blood transplants in patients who have no relation to the donor and are often immunologically mismatched. With bone marrow, this is a risky procedure because it increases the odds that the donor's immune system will reject the foreign marrow, causing severe side effects.

Researchers believe cord blood transplants are less likely to be rejected because infants' immune systems are "naive" and less likely to trigger an immune system flare-up. Wagner also thinks that using cord blood may reduce the risk of infecting the recipient with cytomegalovirus or Epstein-Barr virus—the most common infection in bone marrow transplants—because the placenta may suppress these viruses before they reach the cord.

Finally, cord blood is cheap. McCullough says that it costs about $1000 to obtain and pretest a unit of cord blood, and perhaps another $2000 to complete the tests, many of which can be postponed until the unit is needed. In comparison, it costs $60 to $75 to list a bone marrow donor in the registry, but up to $20,000 to obtain marrow.

Setting the standards

Along with the promise, however, comes a host of potential problems. At a special FDA-NHLBI policy meeting on 13 December, McCullough spoke about the "urgent" need for universal standards to guarantee the quality of cord blood. "You want to give it the best possible chance to succeed," he says. And he hopes FDA will soon establish standards for collecting and storing blood and testing for bacteria, HIV, hepatitis, and blood-borne genetic risks like sickle cell disease, some immune deficiencies, thalassemia, and perhaps even cystic fibrosis. Rubinstein agrees, but warns that it may be hard to reach a consensus—even on basic issues such as how to collect blood—because clinics use different methods.

Beyond such practical concerns lies an ethical minefield that could make FDA's effort very difficult. The main problem is that the donor—a newborn—isn't able to give informed consent, yet the testing of cord blood will create an extensive medical profile, including a partial genetic one, exposing the donor and

the family to risks of privacy invasion.

Transplanters have been aware of these issues for some time but are just beginning to debate them publicly. Kurtzberg and a pathologist at Duke, Emily Reisner, recently teamed up with Duke medical ethicist Jeremy Sugarman to explore some of the dilemmas in the 13 December *Journal of the American Medical Association*. Kurtzberg says, "It's easy to define what the questions are; much harder to define what the answers should be."

The first question facing clinicians is: How far must you go in obtaining consent for banking cord blood? In the past, many have used the blood without consent, because it has been treated as waste. But transplant surgeons attending the 13 December FDA-NHLBI meeting seem to agree that now they must get the mother's consent before collecting cord blood. Some would go further, saying that a parent must explicitly permit certain tests and future uses of donated blood. In addition, some say that any follow-up tests not given consent at the time of donation must receive a follow-up consent.

Once blood has been collected, banks must decide just how much testing should be done, and what should be done with results that indicate an abnormality. McCullough, Kurtzberg, Rubinstein, and others argue that blood banks should maintain not just standard medical files, but genetic data as well. The reason: Infants have no medical history on which to base risk estimates, yet it would be helpful to know whether a blood unit contains a gene for, say, sickle cell anemia or an immune deficiency. Connected to this is the dilemma of whether the family should be told if a test shows that the child carries a dreaded infection (such as HIV) or an abnormal gene. As a pediatrician, Kurtzberg says, her inclination is to inform the family. However, a 1994 Institute of Medicine review recommends that minors not be tested for abnormal genes unless there is "an effective curative or preventive treatment that must be instituted early in life."

There's wide agreement that the donor's privacy must be protected. One solution would be to strip identifiers from donated blood samples and destroy these personal records. But how would blood banks be able to run follow-up tests or contact donors about test results? Some blood bankers—such as David Harris at the University of Arizona, Tucson—say the risks of transferring a genetic disease from a donor to a recipient are minute, certainly no worse than for normal blood donations. Harris, for one, doesn't want to retain such data. Others, such as the Duke team, argue that "moral and medical responsibilities" demand that names not be "delinked" from data.

Federal officials and ethicists have their work cut out for them as they weigh these arguments and try writing guidelines on storing cord blood and data on the donors. As Sugarman says: "We've been talking in hypotheticals" about the risks of maintaining genetic data banks for many years, but "now we're dealing with reality." And if the demand for cord blood transplants increases, as many expect, clinicians will need answers to these once-hypothetical questions.

–Eliot Marshall

ASTRONOMY

Seeking Out Strange New Worlds

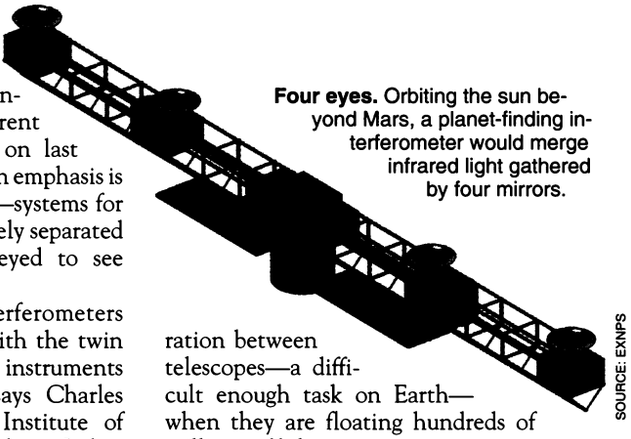
Now that astronomers searching for planets around other stars have detected Jupiter-sized objects, another goal beckons: finding planets more like Earth. That quest is likely to prove even more difficult, however: Indirect clues—regular wobbles in their parent stars—were enough to reveal the giant planets, but recognizing a planet's kinship to Earth would take an image and a spectrum. That doesn't faze National Aeronautics and Space Administration (NASA) Administrator Daniel Goldin, though. He has already organized a planet-search program, called ExNPS, for Exploration of Neighboring Planetary Systems, and last month a "blue-ribbon panel" of prominent astronomers endorsed the quest, which could cost billions of dollars and last 30 years or more.

The panel's report, released quietly during the government shutdown last month, says the discovery of Earth-like planets around nearby stars "would electrify the public imagination and spark a renaissance in science education and science literacy." Led by Nobel Prize–winning physicist Charles Townes of the University of California, Berkeley, the panel also gave its blessing to a plan for pursuing this goal: a version of an ambitious "mission and technology road map" sketched out last summer by three study groups (*Science*, 9 June 1995, p. 1435).

The "road map" approved by the panel reflects an event that overtook the earlier planning: the discovery of a giant planet around a nearby star (*Science*, 20 October 1995, p. 375), followed last month by two more. Detecting alien Jupiters indirectly by observing their parent stars had been the first stop on last summer's map. But now the main emphasis is on developing interferometers—systems for merging the light of several widely separated telescopes—sufficiently sharp-eyed to see extrasolar planets directly.

"First we want to build interferometers at Palomar Observatory and with the twin Keck Telescopes," the 10-meter instruments on Mauna Kea in Hawaii, says Charles Beichman of the California Institute of Technology and the Jet Propulsion Laboratory, one of the contributors to the road map. These instruments, which are already under development with several million dollars in NASA funding, just might be able to see Jupiters around the nearest stars. But in the long run, Beichman says, "if we hope to see Earth-like planets, we'll need an infrared interferometer at 3 or 4 AU [Earth-sun distances] from the sun" to escape the "zodiacal light" of interplanetary dust lit up by the sun. As Beichman sees it, the orbiting interferometer might consist of four telescopes, spaced with a precision of a few angstroms over a distance of perhaps a kilometer.

The panel isn't downplaying the technical challenges, says Caltech's Anneila Sargent, a member of the blue-ribbon panel: "The technical requirements will be developed step-by-step and not overnight." Among the hurdles, the panel notes, is finding a way to maintain the precise separation between telescopes—a difficult enough task on Earth—when they are floating hundreds of millions of kilometers away in space.



Four eyes. Orbiting the sun beyond Mars, a planet-finding interferometer would merge infrared light gathered by four mirrors.

SOURCE: EXNPS

But astronomers argue that the recent planet discoveries leave no alternative to such a system for detecting an alien Earth. Before the discovery, explains planetary expert Tobias Owen of the University of Hawaii, astronomers tended to assume—extrapolating from our own solar system—that Earth-sized planets would likely exist wherever they spotted Jupiter-sized ones. "But these new Jupiter-like planets are so much closer to their sunlike stars than our own Jupiter that we have to conclude that we don't really understand the [planetary] formation process," says Owen. "Hence if we're going to find Earths, we'll really have to *see* them."

–Donald Goldsmith

Donald Goldsmith's book, Einstein's Greatest Blunder: The Cosmological Constant and Other Fudge Factors in the Physics of the Universe, *has just been published by Harvard University Press.*