

minnesota MEDICINE

The New Transplant Patient

Older, sicker patients are now eligible.

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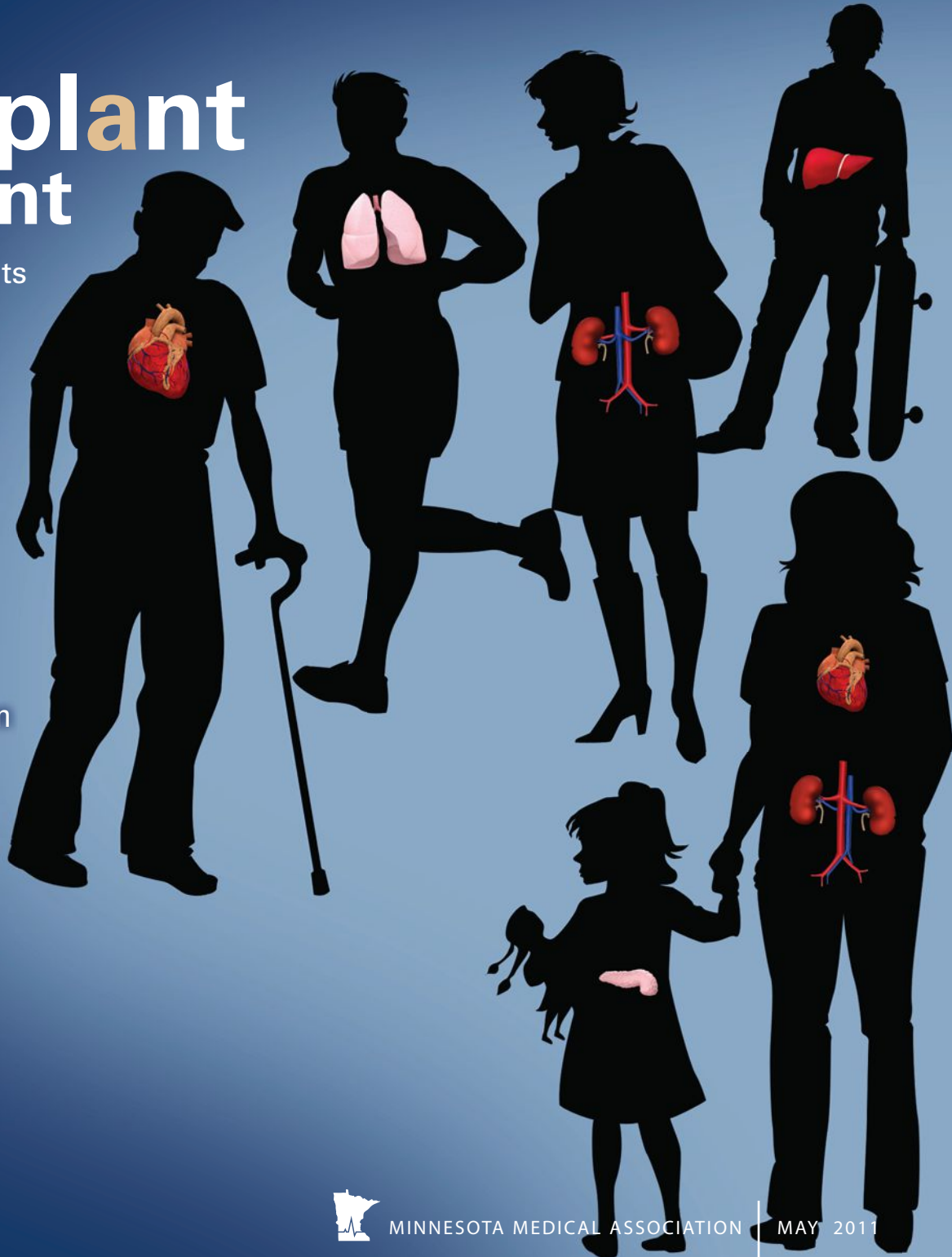
Marrow Matchmaker

The Barbershop Project

Hand Transplantation

PLUS:

Minnesota's Transplant Firsts





COVER STORY

The New Transplant Patient

By Kate Ledger

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Photo by Scott Walker

Fixes for Failing Organs

We're all searching for a solution to wearing out. Time's relentless nipping off of neurons, gelling of joints, and flopping of flesh have provoked patients to invest in potions, health club memberships, and facelifts, and have prompted medical science to seek preventives for organ decline and fixes for organ failure.

Borrowing from the car repair industry's mantra of "if it's broke, replace it," medicine's answer to organ failure for 50 years has been transplantation. Those five decades have seen startling progress in what can be replaced and how well it works after it is replaced. Yet, with that technological progress have come financial and ethical challenges that mirror the dilemmas of health care at large in the United States.

Transplantation medicine's technological strides have been seven-league. Kidney transplants, treacherous treks through perilous rejections and toxic immunosuppressives during the 1960s, are near-routine procedures today, with minimal mortality and impressive survival rates. Those same techniques have brought hearts, lungs, livers, and pancreata into the world of the transplantable and led to successful multiple-organ transplants. Hand transplants and face transplants push the science closer and closer to science fiction. And transplantation medicine is evolving into regenerative medicine as stem cells and tissue-building techniques foresee the day when organs will be rebuilt rather than replaced.

Yet like all advanced medical procedures, transplants are expensive, and in our era of limited resources and deficit-bloating programs such as Medicare and Medicaid, tough questions about what we can afford tarnish the hype about medical

miracles. Not only are more organs being transplanted and more uses for stem cells being found, but more people are "qualifying" for the treatments. In a trend repeated countless times with other medical procedures, as physicians get better at doing them, age limits get liberalized and contraindications melt away. More patients getting transplants means more costs, and the upward, unsustainable cost spiral continues. Even dramatic future medical miracles won't likely find a government "white knight," as the dialysis program did in 1972.

And money is not the only limited resource. The supply of donor organs will not likely meet the demand in our lifetime even if all current recruitment ideas succeed. So we will be left with tough ethical choices that will get even tougher. As people live longer, healthier lives, will there be an upper limit on who gets an organ? Will we eventually ration according to chronological or physiological age? Does everybody have a right to the best and latest medicine has to offer, or do we as a society have to figure out how to say "no" to some patients and families? Will we ever reconcile the debate about when life begins and the use of embryonic stem cells so that some version of that technology with all its promise can move forward? As recent debates about health care reform should remind us, we can't have it all.

So many of these questions boil down to our sense of humanity, who we are and what we expect from this life. Humans will always suffer disease and will always wear out even though medicine of the future will surely modify this. Life has limits, and there is no solution to that.

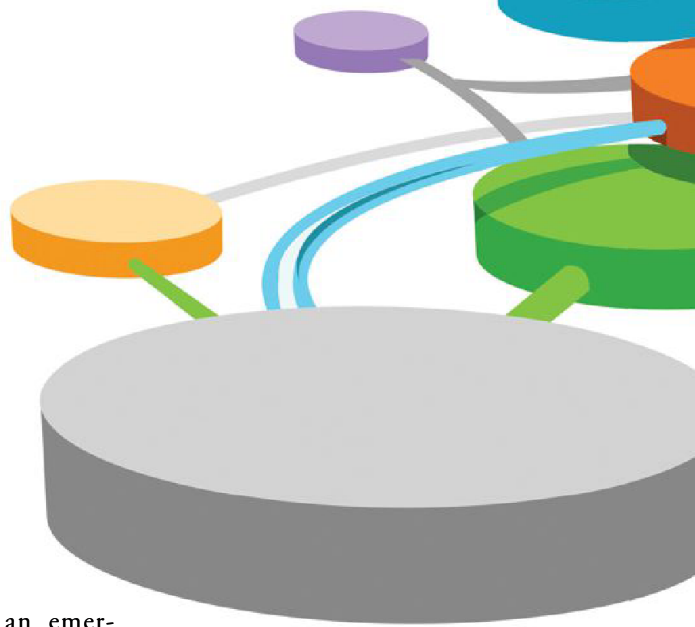
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Charles R. Meyer, M.D., editor in chief, can be reached at cmeyer1@fairview.org

Transplants are expensive, and in our era of limited resources ... tough questions about what we can afford tarnish the hype about medical miracles.

■ Organ Allocation

A Network of Networks

How organ distribution works. | BY CARMEN PEOTA



In terms of complexity, the logistical challenges of organ allocation rival the medical ones of transplantation. In 1984, Congress passed the National Organ Transplant Act, which called for the establishment of a national registry for organ matching. Since then, donors, recipients, and hospitals have been woven into an intricate national web.

The heart of the system is the United Network for Organ Sharing (UNOS), a private nonprofit organization that holds the federal contract to manage allocation. UNOS maintains the allocation registry, which is essentially a huge

database that contains information about potential donors and recipients throughout the United States. UNOS shares information with the nation's 58 regional organ procurement organizations, which work with the hospitals in their area to procure organs and deliver them to transplant centers. The procurement organization for Minnesota, North Dakota, South Dakota, and three counties in western Wisconsin is LifeSource. Last year, LifeSource helped facilitate 500 organ donations.

Here's how the procurement and matching process works: LifeSource receives a call, often

from an emergency room or intensive care unit nurse, when a patient has died or when death is imminent. (Federal law mandates that hospitals report all potential donors to the organ procurement organization for their region.) LifeSource staff evaluate the patient's potential for donation—only 5 percent of people are eligible. If donation is an option, LifeSource sends a staff person to the hospital to talk to the family and gather the medical informa-

tion necessary to determine a match.

The LifeSource staff person enters that information into the UNOS computer system. UNOS then generates a list of compatible recipients for each organ based on allocation criteria for that organ.

LifeSource notifies the appropriate transplant center that an organ is available. The physicians at the transplant center have the right to accept

Where Transplantation Is Done in the Upper Midwest

The following hospitals in and around Minnesota have solid-organ transplant programs.

1 Minneapolis

Abbott Northwestern Hospital
HEART, KIDNEY

University of Minnesota Medical Center, Fairview
HEART, LUNG, KIDNEY, LIVER, PANCREAS, INTESTINE, ISLET CELLS

Hennepin County Medical Center
KIDNEY

2 Rochester

Mayo Clinic
HEART, LUNG, KIDNEY, LIVER, PANCREAS

3 Bismarck

North Dakota Transplant Center
KIDNEY

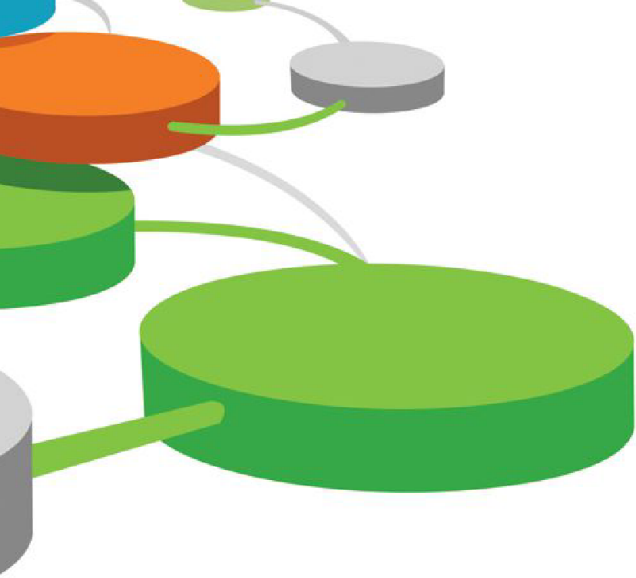
4 Fargo

Sanford Transplant Services
KIDNEY

5 Sioux Falls

Avera McKennan Transplant Institute
KIDNEY, PANCREAS
Sanford Transplant Center
KIDNEY





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or refuse the organ based on their assessment of their patient. If they accept it, the LifeSource staff member or a medical provider will deliver it to the transplant center.

UNOS spokesperson Anne Paschke says numerous factors influence what happens in each case. One is the length of time a particular organ can survive outside the human body, or the “cold ischemia time.” She notes that for lungs, the

cold ischemia time is only two to four hours and for hearts, it’s four to six hours. Livers last up to 18 hours, and kidneys can last as long as 24 hours. Thus, some organs can only be transported short distances. “For hearts and lungs, after we look in your local area, then we’ll look in a 500-mile radius of the donor hospital. There’s just not time to [offer] those organs nationally like there is with livers and kidneys,” she says. ■

National Transplant Leader

In June, Minnesota surgeon John R. Lake, M.D., will become president of the board of directors of the United Network for Organ Sharing, which manages the federal registry and policy-making body known as OPTN (the Organ Procurement Transplantation Network).



John Lake, M.D.

Lake is director of the liver transplant program and executive medical director for solid-organ transplantation at the University of Minnesota.

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John Najarian performing surgery in 2000.

Photo courtesy of the University of Minnesota Medical Center, Fairview

M.D., moderated the discussion with Najarian in March, which traced Najarian's career and highlighted his contributions to the field of transplantation medicine. The following are some excerpts from the talk.

On becoming a surgeon

I didn't want to be an internist who is going to sit around and scratch his beard and think about things. Rather, I wanted to be in a position where I could get something done. Surgery is one of those areas.

On studying immunology after becoming a surgeon

Immunology is what it's all about. Immunology is you. The reason you're able to live in this environment in which you are attacked by various viruses and bacteria is because you have an immunological mechanism that allows you to defend against these things. You're born with it. ... We started out with the wrong idea that a child should be able to receive a transplant without any problem. We learned early that for the first six months, a child has such a strong immune system that he will reject anything so he can survive.

On transplanting adult-sized organs into children

A kidney is as big as a fist. It fills a child's entire abdomen. We had to work out a technique to put them in. The beauty of it is that the kidney shrinks to the size of the child. As the child grows, the kidney grows.

On how long an organ can function

If everything is equal and you don't lose your life because of cardiac disease or cancer or getting hit by an automobile, you are destined to live 120, maybe 125 years. So if you take out an organ from someone who is 90 years old, it has 30 years to go. A lot of people don't think about that. ... We have transplants [organs] that are over 100 years of age.

■ Transplantation Leader

In His Own Words

Transplant legend John Najarian on his life and work. | BY KIM KISER

The University of Minnesota's Witness to History lecture series recently featured John Najarian, M.D., a surgeon who put Minnesota on the map during the 1970s and '80s as a leader in organ transplantation. Under his guidance, the University of Minnesota earned a reputation for performing transplants in high-risk, medically complex patients who would have been turned down elsewhere, including children, older adults, and diabetics.

Najarian was involved in a number of transplantation firsts—including the world's first transplant of insulin-producing islet cells from a deceased

donor, of a partial pancreas from a living related donor, and of islet cells from a living donor. He also is known for developing the anti-rejection drug ALG (anti-lymphocyte globulin). He became embroiled in a scandal related to the handling of its manufacture and sale; in 1996, federal charges brought against him were thrown out. By then, Najarian had resigned from his position as head of the department of surgery at the university. But he remained on the faculty, and at age 83 he still does surgery and research.

Assistant professor of family medicine and community health Jon Hallberg,

About medicine and surgery becoming so specialized

I was a general surgeon. Sixty to 70 percent of the things I did were general surgery. I tried to train my people that way. If you get into a situation where you're doing a transplant and there's a problem and you have to resect a bowel, you don't want to have to call someone in to do it. I want you to be a general surgeon who does transplantation. I do not want you to be a transplant surgeon. Unfortunately, that doesn't work now.

On retirement

If you enjoy what you're doing, why leave? ... I think once you do retire you must be very careful. It's so easy to get into the

position of watching television and reading books and what not and not getting involved with people and being part of the communication cycle. I think that leads to what we call senile dementia.

On his current research

We're looking at organs from other species. We're raising pigs here that ... are totally clear of bacteria or disease of any sort. ... It won't be long until we're using pig organs, starting with kidneys and from there livers and pancreases.

The other place we can go is to stem cells. Hopefully, we'll be able to educate and guide them to make things like insulin. We're not standing still. ■

At a Glance

- Appointed professor and chair of the department of surgery at the University of Minnesota in 1967; named Regents Professor, the university's highest honor, in 1986
- Admitted to the Royal College of Surgeons in England in 1987
- Recipient of the 2004 Medawar Prize, deemed the world's most prestigious for outstanding achievement in organ transplantation
- Has done more than 6,000 solid-organ transplants
- Has published more than 1,300 articles

Source: Najarian J. *The Miracle of Transplantation: The Unique Odyssey of a Pioneer Transplant Surgeon*. Phoenix Books, Inc. San Francisco. 2009.



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■ Organ Donation

A Shave, a Haircut—and a Kidney?

Barbers teach African-American men about organ donation and the importance of attending to their own health. | BY TROUT LOWEN

The body is a lot like a vehicle, Mr. B likes to tell customers while he clips, snips, and trims their curly locks into the latest fade, shade, or flat top.

In between talk of the Twins, Vikings, and Timberwolves, Mr. B, also known as Bilal Saleem, a master barber at the Gifted Handz salon in St. Paul, talks about his own efforts to take better care of himself and the reasons his clients should, too.

“Your car, if you don’t have gas in it, then it’s not going anywhere,” he says. “If you don’t check to see if your battery is up to par, then it’s not going to last long. And if you don’t have the right amount of oil in it, your engine can blow up.”

Although his analogy may seem a little unorthodox, Mr. B’s folksy wisdom about good health is something his clients—African-American men—can relate to. And it’s something many of them need to hear. “I’ve had battles of my own, and I see the needs of others in the African-American community,” Saleem says. “Information [about healthy living] is out there, but it’s not really at the level where it needs to be.”

That’s one of the reasons Saleem agreed to participate in Barbershop Conversations, a three-year initiative to im-

prove health and increase the number of African-American men in the Twin Cities who are organ donors. The project, jointly sponsored by LifeSource, the University of Minnesota, and Q Health Services, has involved 26 barbers at 18 barbershops in Minneapolis, St. Paul, and the Twin Cities suburbs. Modeled after similar initiatives around the country, it initially focused on using barbers to provide culturally specific, community-based education about organ donation. The barbers now also provide information about diabetes, hypertension, and obesity.

As a group, African-Americans have higher rates of these conditions, which contribute to kidney failure, than the general population and lower organ donor rates—about 10 percent lower than the majority population, explains Susan Mau Larson, public relations director for LifeSource, which coordinates organ and tissue donation in the Upper Midwest. African-Americans also make up a disproportionately high percentage of those on the transplant waiting list (see “The Need for African-American Donors”).

It’s a difficult population to reach through traditional public health channels, however. Many African-American men don’t visit the doctor regularly, and many distrust the medical

The Need for African-American Donors

In Minnesota and across the country, African-American men have lower organ and tissue donation rates than the majority population and lower rates than African-American women.

Overall, about 55 percent of Minnesotans have an organ-donor designation on their driver’s license. Women have the highest rate, around 55 percent. The average rate for men is about 45 percent. The rate for African-American men is closer to 35 percent, according to David Radosevich, Ph.D., an epidemiologist and assistant professor in the University of Minnesota’s department of surgery.

At the same time, Afri-

community. Barbershops are gathering places where very open and honest conversations often take place, Larson says. Saleem agrees. He’s known some of his clients for nearly 20 years. They come in for a haircut and stay for coffee and conversation.

The barbers who par-



can-Americans are disproportionately represented on the transplant waiting list. In Minnesota, African-Americans make up about 8 percent of the state’s population but represent closer to 16 percent of the patients waiting for a transplant, Radosevich says. That is because they also have higher rates of the diseases that can lead to organ failure such as diabetes and hypertension.

ticipated in the project were taught how to engage clients in ongoing discussions about health and ultimately about organ donation. And they were paid for their participation and for each donor recruited. A total of 362 men participated in the project; their average age was 40 years.



Photo courtesy of LifeSource

Barbers at TC Cutz in Crystal have been educating their customers about health issues and organ donation.

Nationwide and in Minnesota, African-Americans are five times more likely than whites to develop end-stage renal disease and require a kidney transplant. Of the 362 men who took part in the Barbershop Conversations project, an effort to increase the number of African-American men who are organ donors, 55 percent had at least one of the antecedent risk

factors for renal disease: hypertension, diabetes, or a body mass index of 30 or above. Radosevich called that finding “alarming,” given that the average age of the participants was around 40.

“That’s a very high percentage with a pre-existing health condition that would predispose them to kidney problems down the road,” he says.—T.L.

A Question of Trust

From the outset, one of the project organizers’ biggest challenges was building trust, both with the barbers and their clients, says David Radosevich, Ph.D., an epidemiologist and assistant professor in the University of Minnesota’s depart-

ment of surgery and the lead researcher on the project.

Radosevich says when he first walked into the barber-shops, some of the owners suspected he might be “po po” (slang for police), and one thought he was trying to collect alimony. There was also mistrust of the project, he says.

Often, one of the first issues to come up in conversation was the Tuskegee syphilis study, conducted by the U.S. Public Health Service between 1932 and 1972. Many of the early discussions with the barbers, he says, were about convincing them that the university wasn’t recruiting for an experiment.

Clarence Jones, director of Q Health Services, the outreach arm of Southside Community Health Services, says the researchers had to earn the barbers’ trust. “We had to spend a lot of time up front being transparent, being open, and answering questions,” he says.

Radosevich says they also had to dispel misconceptions about organ donation. Many participants were concerned that as organ donors they might receive substandard medical care in an emergency.

That isn’t just a concern among African-Americans, however, Radosevich says. He’s heard the same concern expressed by his 30-year-old son. Others were convinced that organs donated by African-Americans would likely go to white patients. He says the opposite scenario is more likely because there are proportionately more African-Americans on the transplant waiting list and because certain antigenic alleles are more common within certain racial groups, which makes a black-to-black or white-to-white match slightly more likely.

Although many of the participating barbers had experience with transplantation through a family member—one was even planning to be a living kidney donor for his sister, broaching the topic of organ donation was still difficult. “What we ended up doing was focusing the early part of our intervention on questions about chronic disease that are more salient in the black community,” Radosevich says.

The Results

Preliminary findings show only a small increase in the rate of organ donation. But the \$350,000 project, funded by a grant from the U.S. Health Resource and Service Administration and supported by the Pan African Community Endowment of the St. Paul Foundation, is still being viewed as a success.

Participants were asked to fill out a survey at the beginning and end of the project to assess their views of organ donation.

At the end of three years, both barbers and clients were more willing to consider donation, were more informed about donation, and were more willing to talk about donation with friends and family. They were also better informed about the risk factors for chronic disease and lifestyle changes that could improve their health.

“You didn’t see a huge change in terms of the numbers according to the state registry because most of the people change their choice when they get their [driver’s] license renewed. But we definitely have story narratives and other kinds of indicators that say that attitudes of people have changed,” Jones says. “That’s all you want.” ■

Enter Minnesota Medicine’s photo Contest



see www.minnesotamedicine.com/photocontest for details



Photo courtesy of the National Marrow Donor Program

■ Blood and Marrow Donation

The Matchmaker

Headquartered in Minneapolis, the National Marrow Donor Program has become the world’s resource for patients needing a marrow, cord blood, or peripheral blood transplant.

| BY KIM KISER

In a single-story warehouse in New Brighton, the 14 employees of the National Marrow Donor Program’s (NMDP) repository are getting ready for the morning FedEx delivery. More than a dozen tubs will arrive, each containing envelopes that hold cotton swabs with cells from the lining of the cheeks of potential bone marrow donors that will need to be catalogued, tissue-typed, and stored. Those cells, along with blood samples, are the blocks on which the program’s donor registry is built—bits of tissue that have lifesaving potential for people with more than 70 blood and metabolic disorders.

Since the registry began matching donors and recipients in 1987, the number of samples stored at the repository has grown to more than 10 million (see “The Repository”). Leila Jones, Ph.D., who manages the repository, says they will store the samples until they are no longer good for tissue typing. “We haven’t found that endpoint yet,” she says.

In many ways, the repository’s growth is a reflection of the way science has changed blood and marrow transplantation. “We’re not just about marrow, we’re about peripheral blood stem cells, marrow, and cord blood, and at \$325 million in annual revenue

and 720 employees, we’re not just a program anymore,” says CEO Jeff Chell, M.D. “We’re not national anymore, we’re international.”

Last year alone, the NMDP facilitated 5,200 blood and marrow transplants (about half involved donors or recipients from outside the United States)—more than three times the number performed in 2000, the year Chell became head of the organization. And when Chell peels off those statistics, his enthusiasm for his work come through loud and clear. So does the reason for it: “We can all trace what we do to saving lives.”

Inside the walk-in cooler, where blood samples are stored and temperatures are held at -20F.

A Broader Approach

Before Chell joined the NMDP, which is headquartered in northeast Minneapolis just a few miles from the repository, the organization's primary function was collecting names and samples from potential marrow donors. That had been the organization's mission since the 1980s, when marrow transplantation from unrelated donors became a viable treatment for blood diseases such as chronic myeloid leukemia and lymphoma.

When Chell, an internal medicine physician who had run the clinic division of Allina Health System and worked with cancer patients in his practice, took the helm, his

first task was to identify what else the organization could do. "Rather than thinking of ourselves as a donor registry, we needed to think of ourselves as

an advocate for patients, helping our transplant centers any way we could to provide better care for patients," he explains, adding that the program cur-

rently works with 169 transplant centers in the United States as well as centers in 12 other countries. In addition to maintaining the registry, the

The Repository

The National Marrow Donor Program has been collecting and storing samples of blood and tissue since 1987. Today, those samples are housed in a 35,000-square-foot warehouse in New Brighton that's equipped with floor-to-ceiling storage bins for buccal swab and filter-paper samples of tissue, a walk-in freezer where the temperature is held at -20F for storing blood samples, 30 upright industrial freezers that reach -80C, and 20 cryogenic liquid nitrogen tanks that reach -180C for storing research samples.

Here's a snapshot of the facility:

- Total samples stored: 10 million-plus
- Number of samples received each month: 37,000
- Number of sample sets added each year: 400,000-plus
- Donor/recipient pairs whose blood samples are stored for research: 22,000



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Pediatric Update Conference - Beyond the Basics	October 29, 2011
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Otolaryngology Conference	November 18, 2011
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NMDP conducts research and provides education and services for patients and physicians (see “Five Things Doctors Should Know about Blood and Marrow Transplantation”).

Thinking differently is only part of the explanation for the organization’s growth and evolution, however. At first, chronic myeloid leukemia was the reason for most marrow transplants. By the mid-1990s,

the patient’s chance of becoming ill or dying from the pre-treatment. The second was the introduction of peripheral blood stem cells. Using stem cells collected from the peripheral blood stream rather than from marrow allows for more rapid blood count recovery and outcomes similar to those of marrow recipients; it also promotes faster engraftment or production of new cells. “The

talk to people about the idea of saving a life rather than simply joining a registry. “We started setting goals of growing by 10 or 20 percent a year, and the network responded to those goals,” he says.

Perhaps the biggest boost to donor recruitment was the development of buccal swab testing, which allows potential donors to simply wipe the inside of their cheek to obtain

find the best match,” Chell says. So in 2005, the organization became the national coordinating center for cord blood, adding information about cord blood units from 26 banks around the world to the registry. “We did maybe zero cord blood transplants in 1999. This year, we’ll do 1,200—and that will account for more than 20 percent of all of the transplants we facilitate,” he says.

According to Chell, the NMDP’s next priority will be to enhance the organization’s IT systems. With each additional partnership or service—adding peripheral stem cells and cord blood to the registry and working with new international transplant centers and registries—has come more data and more paperwork (it’s not uncommon, he says, to receive 60-page faxes from international partners looking for a matching donor). Chell says they would like to build a system that would allow transplant centers anywhere in the world to call up information about potential donors online. He explains that having such access will become critical as more uses are found for marrow, peripheral stem cells, and cord blood and as more patients become eligible for transplantation.

“We are preparing ourselves for a future in which the number of transplants may go up at least threefold or greater,” he says. “We want to build a system that could manage up to 100,000 transplants a year, and I believe we have the resources to accomplish what we need to accomplish.” ■

Birth of a Registry

In the early 1980s, when transplantation using unrelated donors became feasible, families of patients began creating their own informal registries of family members, friends, and acquaintances in order to find a match. Soon, those families began combining their lists.

Working with representatives from Red Cross agencies, which were tissue-typing platelet donors, and doctors from the University of Minnesota, Memorial Sloan-Kettering Cancer Center, the Fred Hutchinson Cancer Research Center, and other institutions that were treating leukemia and lymphoma patients, and with \$2 million from the federal government, they built a national registry in 1987. They located it in Minneapolis after the University of Minnesota and St. Paul Red Cross agreed to provide staffing, space, and computer systems. The National Marrow Donor Program now operates independently.

research was showing that transplantation held potential for other diseases such as acute myelogenous leukemia and myelodysplastic syndrome. “We didn’t understand how many patients could really benefit from transplant,” Chell admits.

In the late 1990s, two developments opened up transplantation as a possibility for older patients. One was the introduction of reduced-intensity conditioning, in which patients receive lower doses of chemotherapy and radiation prior to transplant—the idea being that it reduces

combination of using reduced-intensity conditioning plus this new form of therapy—peripheral blood stem cells—allowed us to expand the patient population to people well beyond age 50, to people who were sicker, and to more fragile patients,” Chell says.

New Challenges

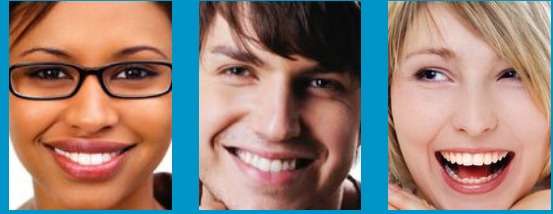
With the ability to treat new patients and diseases came the need for more sources of blood and marrow. In addition to rebranding the registry as the Be the Match Registry in 2009, Chell has increased the number of recruiters, who

squamous cells that can be precisely tissue-typed. Potential donors can register online, have a buccal swab testing kit sent to them, swab their mouth, and send the sample back. No blood draw required until a potential match is identified.

Another breakthrough that significantly affected the supply of available cells—and the work of the NMDP—was the ability to use cord blood. Cord blood banks had been working independently, so looking for a potential match involved contacting each individual bank. “Transplant coordinators were saying it took all their time to

Five Things Doctors Should Know about Blood and Marrow Transplantation

1. It's effective for more than 70 medical conditions, says Jeff Chell, M.D., CEO of the National Marrow Donor Program in Minneapolis.
2. Cells are available. "We can find an adult or cord-blood match for the vast majority of Americans," he says. In 2006, more than one-third of allogeneic transplants performed used cells from unrelated donors.
3. Transplantation isn't the treatment of last resort. "Early referral is important," Chell says. "Outcomes are best when people are treated early in their disease."
4. There is no age limit for transplantation. "We've transplanted people from 0 days to 82 years of age," he says.
5. There is an optimal time for transplantation. Although it differs according to disease, it's usually during the first remission, Chell says. Guidelines are available at www.marrow.org/md-guidelines in the Physicians' Resource Center. Apps are available for the iPhone, Android, Blackberrv. and iPad.



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■ Bundled Billing

Learning from Experience

The government is exploring bundled billing—a practice long used in organ transplantation—as a strategy for reducing health care costs. | BY CARMEN PEOTA

In January, a Government Accountability Office (GAO) report to Congress on the feasibility of using bundled payments to reduce escalating Medicare costs noted that bundling payments had been the “industry norm” for organ transplantation for two decades. Bundling is a billing/payment strategy that results in a single payment being made for a group of services related to an episode of care, potentially involving several providers. The bundled payment approach has been suggested as a way to contain costs in both state and national debates about health care reform.

Minnesota’s 2008 health care reform legislation proposed a bundled-payment approach called “baskets of care.” The federal government is piloting bundled-billing projects for Medicare.

The GAO investigators interviewed representatives from five of the nation’s largest payers—Aetna, Cigna, Humana, UnitedHealth Group, and Wellpoint—and from physician groups about their experience with bundled payments to learn how the process works. The payers reported that they typically signed contracts with hospitals that met their criteria for volume of

surgeries done and outcomes. And they typically bundled claims for hospital, physician, and ancillary services provided before, during, and after a transplant. The payers pay the hospitals, which then pay the physicians.

The payers told the GAO group that bundling works for transplants for a number of reasons: They are high-cost procedures, which increases the potential for savings; they have clearly defined start and end points, which aids in defining an episode of care; and they have well-established care protocols and outcome measures.

How It Works

To better understand the ideas behind and mechanisms required for bundled payments, I spoke with Sidney Fiergola, J.D., who negotiates organ and tissue transplant-related contracts for the University of Minnesota Medical Center, Fairview.

Fiergola says bundled billing emerged as organ transplantation became more common and insurance companies sought ways to contain costs. Insurers decided to contract with transplant centers that met certain criteria through special networks. The idea behind that contracting arrangement was that payers would pay lower rates in exchange for the network driving traffic to the transplant center.

About a dozen networks currently mediate the contracts between the nation’s transplant centers and payers, which range from traditional insurers to companies that self-fund health coverage. Cigna’s LifeSOURCE Transplant Network, for example, has contracts with more than 500 transplant programs at more than 120 facilities.

Fiergola says that initially the payment bundles covered the period from the time a patient was identified as a potential transplant candidate through the year following transplantation. But hospitals quickly realized that a single payment for the care delivered over such a long period of time put them at significant financial risk. “In some parts of the country, a kidney patient can wait six to seven years for a transplant. Managing a patient that long would be burdensome,” Fiergola explains. Now,

the transplant bundles are for a defined (and shorter) period of time, usually a period of weeks rather than years.

Billing for transplants done through the University of Minnesota starts with the medical center, which has a system for flagging charges as soon as a patient is identified as a transplant candidate. The physician group that provides the medical and surgical services submits claims to the hospital, which bundles those with its own claims and submits them to the payer. To stay on top of this, the hospital has three staff members who track claims for the 600 or so solid-organ and blood and marrow transplants it does a year. “It’s extraordi-

narily complicated,” Fiergola says.

Feasible for Other Procedures?

Although the GAO report’s authors didn’t rule out the feasibility of using bundled payments for other services, they noted factors that might hinder wider adoption: the fact that it requires a manual claims process (all five payer representatives said processing claims for bundled payments was too complex for their automated systems), that standard definitions for an episode of care do not exist, and that patients’ choice of providers is limited.

Fiergola is also somewhat skeptical that the bundling

strategy can be widely applied. She believes the administrative burden would be too great if bundling were used for higher-volume procedures such as knee replacements. “The payment systems are not set up to align that way currently,” she says. “If you do 5,000 of some procedure, getting the people power to monitor this manually would be costly.”

She notes that although Fairview will continue to bundle claims for transplant services “because that is where the market is currently,” the organization places more stock in a “total-cost-of-care” approach to cost-containment, which she describes as managing a patient, not just one problem.

Julie Sonier, who worked on the baskets-of-care idea for the Minnesota Department of Health and is now deputy director of the State Health Access Data Assistance Center, says bundling is probably most workable in a system that is more integrated. For one thing, less integrated groups of providers will struggle to decide who will take the lead in administrating the process. “Maybe one reason bundling is common for transplants is because the only people who do them are large integrated services,” she says. “They can figure out how to do it.” ■



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Estimated Average First-Year Billed Charges Per Transplant

United States, 2008

Transplant	30 Days Pre-transplant	Procurement	Hospital Transplant Admission	Physician Charges During Transplant	Admission 180 Days Post-transplant	Immuno-suppressants	Total
Heart	\$34,200	\$94,300	\$486,400	\$50,800	\$99,700	\$22,300	\$787,700
Single Lung	\$7,500	\$53,600	\$256,600	\$27,900	\$84,300	\$20,500	\$450,400
Double Lung	\$20,700	\$96,500	\$344,700	\$59,300	\$113,800	\$22,800	\$657,800
Heart-Lung	\$49,100	\$151,900	\$682,500	\$73,000	\$143,300	\$24,700	\$1,123,800
Liver	\$21,200	\$73,600	\$286,100	\$44,100	\$77,800	\$20,600	\$523,400
Kidney	\$16,700	\$67,500	\$92,700	\$17,500	\$47,400	\$17,200	\$259,000
Pancreas	\$16,500	\$68,400	\$93,400	\$16,300	\$58,700	\$22,200	\$275,200
Intestine	\$48,400	\$77,200	\$743,800	\$100,600	\$124,300	\$27,500	\$1,121,800

Source: United Network for Organ Sharing

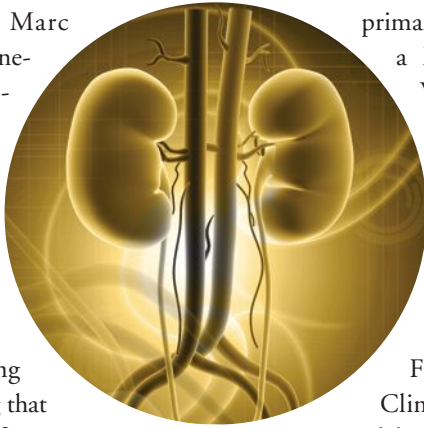
■ Chronic Kidney Disease

Commonly Good Care

Fairview doctors are working to make early diagnosis and better management of chronic kidney disease routine and dialysis rare. | BY CARMEN PEOTA

Five years ago, Marc Weber, M.D., a nephrologist with University of Minnesota Physicians (UMP), began to realize that doctors could do better at caring for patients with chronic kidney disease (CKD). Growing evidence was showing that better management of patients with both early and late-stage disease resulted in better outcomes.

So when his boss, UMP CEO Bobbi Daniels, M.D., also a nephrologist, pitched the idea of developing a systematic approach to managing patients with kidney failure, Weber was more than willing to take the lead. Since then, he's been spearheading an effort to overhaul the way he and his colleagues care for patients with CKD. The effort involves InterMed Nephrology Group, an independent medical group, along with UMP nephrologists and primary care providers, all of whom work at Fairview Health Services' clinics. "What makes this unusual is that we are trying to link multiple nephrology practices, multiple



primary care clinics, within a huge care system," Weber said last year in an article in the newsletter *Nephrology Times*.

Working with Angela Dhruvan, M.D., a primary care physician at Fairview Hiawatha Clinic, Weber developed guidelines around issues such as when patients should be referred to specialists and how to better manage complications of CKD. They then got the protocols embedded in Fairview's electronic health record (EHR). Now, when a patient's glomerular filtration rate is below 30, for example, the EHR prompts the doctor to refer that patient for evaluation by a nephrologist. In the past, he or she may have waited until the patient was close to needing dialysis, thus missing out on the chance for a pre-emptive kidney transplant, which, he says, is the best way to treat end-stage kidney disease.

The goal, Weber says, is to get patients on track for a transplant sooner. "Dialysis is the last resort in my mind." ■

■ Transplant Data

Minnesota's Registries

In September of 2010, the Minneapolis Medical Research Foundation (MMRF) won a multimillion dollar contract from the federal government to maintain and analyze data on solid organ transplantation in the United States.

Through the new Scientific Registry of Transplant Recipients, researchers from the foundation will conduct analyses that will support the development of regional and national policies regarding distribution of organs including hearts, lungs, kidneys, livers, pancreata, and intestines. They also will evaluate the current policies of the national Organ Procurement and Transplant Network, patient outcomes and transplant center performance, and transplant-related costs.

The registry is part of the MMRF's Chronic Disease Research Group, which also serves as the coordinating center for the North Central Donor Exchange Cooperative, a collaboration between kidney transplant centers in the Upper Midwest designed to match a donor and recipient who are incompatible with each other to another donor-recipient pair in a similar situation; and the United States Renal Data System, which collects, analyzes, and distributes data about end-stage renal disease in this country.

■ Kidney Transplantation

Damage Assessment

A Mayo Clinic study of kidney transplant recipients shows progressive damage to transplanted kidneys may be less severe and less common than previously reported.

The study involved 797 patients who received kidney transplants at Mayo between 1998 and 2004 and were followed

for at least five years post transplantation. A subgroup of 296 patients had biopsies done one and five years following their transplant.

Eighty-seven percent of those patients had mild or no signs of scarring to the transplanted organ one year after transplantation, and 83 percent had simi-

lar results five years out.

Reports from the early 1990s showed that a majority of patients had progressive scarring that ultimately led to failure of the new kidney.

The findings were published in the April 2011 issue of the *American Journal of Transplantation*.



Patricia J. Lindholm, M.D.
MMA President

Respect is the
foundation of
collegiality and the
main thing we need
to focus on.

Photo by Steve Wiewerka

The Case for Collegiality

Collegiality is the “cooperative interaction among colleagues.” That definition sounds appealing, doesn’t it? And there are good reasons. Collegiality is a recipe for patient safety and the highest quality health care. It’s also a powerful force when it comes to our own well-being. Why is that the case? Physicians who have collegial professional relationships can draw on each others’ expertise in order to help patients and find support when they need it.

I believe, however, that the concept has been somewhat neglected in the medical curriculum and in medical practice.

During my years as a medical student and resident, it was common to hear attending physicians denigrate entire specialties. It was not unusual to see instruments thrown in operating rooms. Students were routinely humiliated in front of their peers, nurses, and even patients. Sexual harassment of female students and residents was pervasive. (I did not train in Minnesota, of course.) I’d like to ensure that these things never happen again.

I suspect that most of us, even those of us in small communities, interact with medical students. I think it’s imperative that we all model collegiality to those we teach.

Respect is the foundation of collegiality and the main thing we need to focus on. Students who witness truly respectful interchanges among physicians will be more likely to have respectful relationships with their colleagues once they start practicing.

Patients expect the members of their

health care teams to be collegial, and they are right to do so. I believe patient safety is compromised when we do not behave respectfully toward one another. One of the more dangerous ways physicians fail to show respect is by not communicating with peers or doing so poorly. A consultant who does not convey her thoughts to a referring physician is not only doing that physician a disservice, she is doing a disservice to the patient. Likewise, a referring physician who is not clear about the reason for a consultation is not only wasting the time of another professional but is also failing the patient.

The truth is, we all need each other if we are to provide patients with the best possible care. We need the “big picture” expertise of generalists and the depth provided by subspecialists. We need the procedural experts and the cognitive ones.

One valuable aspect of membership in the MMA is that it provides so many opportunities for physicians to come together. During meetings and events, we are bridging the metro-outstate, academic-community, and primary care-subspecialty divisions that undermine collegiality.

I think we physicians can set an example for society at large. Our recent history in this country has been marked by a lack of civility in the political, business, and community spheres. Labeling and demonizing have become endemic in the media and in the community. I’d like to see us take the lead in changing the culture.

Let’s start by improving our own culture. Our students and our patients are counting on us.

Physicians Generate Jobs in Minnesota

Minnesota's office-based physicians have a significant financial impact on the state's economy, according to a study conducted on behalf of the American Medical Association. Office-based physicians generated \$16.3 billion of direct and indirect economic output in their communities in 2009.

The study, which was funded in part by the MMA, assessed the economic impact of office-based physicians who are actively practicing (not those who are working in other professional areas such as research, are residents, or who have full-time hospital-based practices). The report breaks down the findings by state. In 2009, Minnesota's 11,688 office-based physicians accounted for about 84 percent of practicing physicians in the state. Those physicians directly or indirectly supported 67,483 jobs, including their own. (The full report is available at www.mnmed.org/economicimpact.)

"Although physicians are primarily focused on providing excellent patient care, physician offices and the jobs and revenue they generate are significant contributors to state economies," says Patricia Lindholm, M.D., MMA president. "This study illustrates what people in Greater Minnesota already know, which is that having physicians not only helps the health of patients, but also helps the economic health of communities."

The study also found office-based physicians supported \$12.1 billion in wages and benefits, and generated \$761 million in state and local taxes in Minnesota. In addition, Minnesota hospitals generated about \$8.4 billion in wages and benefits; nursing homes and residential care facilities, \$3.5 billion; and colleges, universities, and professional schools, \$1.6 billion, according to the report.

MMA staff are sharing the results of the study with lawmakers in conversations about the potential economic impact of proposed cuts to the health care safety net. In April, the Minnesota House and Senate passed budgets that would reduce health

Metro area	Doctors	Jobs their practices generate
Duluth	680	3,784
Fargo	466	2,649
Grand Forks	216	1,201
Minneapolis/ St. Paul	7,282	41,982
Rochester	1,811	10,177
St. Cloud	406	2,310

Source: The State-Level Impact of Office-based Physicians: Overview Report. American Medical Association. 2011.

care spending over two years by as much as \$1.8 billion. Both budgets also would result in the loss of more than \$1 billion in federal matching funds because they would repeal the Medicaid expansion Gov. Mark Dayton authorized to take effect March 1. "When you consider that physicians, nursing homes, and hospitals support about

\$25 billion in wages and benefits, taking more than \$2.5 billion out of the state's health care economy, as GOP lawmakers are proposing, is obviously going to cause financial hardships for these providers and the communities that rely on those jobs," says Dave Renner, the MMA's director of state and federal legislation.

MMA and TCMS Launch Insurance Agency

In March, the MMA and Twin Cities Medical Society (TCMS) launched an insurance agency designed to provide members with a one-stop shop for individual and group insurance products such as long-term care, disability, life, and health coverage. Called MMBR Insurance Agency, it will be part of Minnesota Medical Business Resources, a for-profit company owned by the two medical societies. Barry Weber will serve as director of the new agency.



Weber says the MMA and TCMS researched the market to find the best products and secure discounts for members. "The advantage that we can offer is that we understand physicians and their needs," Weber says. "We've done the legwork to find the best products so you don't have to."

For further information or help finding insurance, contact Weber at bweber@mnmed.org or 612/362-3702 or visit www.mnmed.org/insurance.

MMA Annual Meeting Gets a New Look

The MMA's Annual Meeting is undergoing some changes this year. For one thing, the meeting will be shorter. In addition, the resolution process will be streamlined. The changes were called for in Resolution 106, which was adopted by the House of Delegates last year.

Here's how the new process will work: The deadline for submitting resolutions this year will be July 1. A Resolution Review Committee, which will be composed of eight members including one from each of the six MMA trustee districts plus the speaker and vice speaker of the House of Delegates, will review the resolutions and recommend whether they should be

- referred to a House of Delegates reference committee,
- referred to the MMA Board of Trustees,
- rejected or returned to the component medical society sponsoring them, or
- reaffirmed as existing MMA policy.

In August, registered delegates will have the opportunity to vote electronically on the Resolution Review Committee's recommendations. Resolutions will be sent to a reference committee for further consideration if at least 25 percent of regis-



Photo by Steve Weverka

T. Michael Tedford, M.D., at the 2010 Annual Meeting.

tered delegates submit such a request.

The electronic vote will replace the opening session of the House of Delegates. The change not only will make the meeting shorter but also will make it easier for physicians to participate.

Delegates must register by early August to participate in the electronic voting

process. Please contact your component medical society or specialty society as soon as possible if you are interested in serving as a delegate.

If you would like to serve on the Resolution Review Committee, please contact us at am@mnmed.org.

MMA Annual Meeting Features Keynote on Resilience

Robert Veninga, Ph.D., author and professor emeritus at the University of Minnesota School of Public Health, will deliver a keynote address on resilience in medical practice at the MMA's 2011 Annual Meeting.

Veninga, who has published four books and more than 100 articles on resilience, innovation, and leadership, will share his perspective on how physicians can care for themselves while caring for others. He will answer questions such as How do you stay resilient when work demands increase? and How do you stay upbeat when there is conflict at work or with patients?

The Friday morning event is open to all members and has been approved for *AMA PRA Category 1 Credit*™.

Veninga is a member of the Teachers Hall of Fame at the University of Minnesota and is a frequent speaker at national and international conferences.



MMA 2011 Annual Meeting

Duluth Entertainment Convention Center

September 15-16, 2011

To learn more, go to www.mnmed.org/annualmeeting

■ Meet a Member

Ed Ratner, M.D.

Ed Ratner's professional goals were born of personal tragedy.

Ed Ratner is on a mission to change end-of-life care in Minnesota. And to Ratner, that means helping people care for their dying loved ones at home.

The geriatrician's interest in end-of-life and home care developed unexpectedly in the 1990s when his then 9-month-old daughter Ilana was diagnosed with an untreatable, terminal neurological illness. As a physician, he knew the demands that lay ahead. Yet, he and his wife wanted to care for their daughter at home and made that a priority.

Over the next two and a half years, he learned about end-of-life care as a caregiver and father rather than as a doctor. And he and his wife grew to appreciate the services of the home care and hospice nurses, therapists, chaplains, and volunteers. "In 1995, Ilana died at home, in our arms, never having spent a night in the hospital," he says.

As Ratner grieved, he found a new personal mission: to make care like that his family received available throughout the community. At Allina Health System where he worked, he led an initiative to offer home-based care to patients nearing the end of life, and to make a bereavement-support program previously available only to families of hospice patients available to patients systemwide. He also organized a statewide end-of-life collaborative that released a report in 2002 establishing a framework for initiatives across the state. In 2008, he joined the MMA's Ethics Committee and worked to develop a Provider Orders for Life Sustaining Treatment (POLST) form for the state. That form is already being widely used in Minnesota. "This has only been in circulation for about a year, and the last I heard, about half of the nursing homes in the state are using it," Ratner says.

One of the lessons Ratner has learned as he's worked on home-care and end-of-

life care issues is to involve others. "The individual physician can take care of patients one by one, but it doesn't appear to me that you can make communitywide or political changes [alone]," he says. "To do that, you need people coming together and agreeing to do something, and that requires an organization like the MMA that has legitimacy and broad membership." He says organized medicine enables physicians to leverage a large group in order to make things happen.

In addition to working on statewide policy, Ratner continues to see patients through his practice, House Call Specialists. He almost exclusively cares for patients who cannot easily leave their homes because of advanced age or multiple illnesses. And in his role as a University of Minnesota Medical School faculty member, he trains medical students to do home visits. In 2009, he created a residential service learning experience for medical students, where they lived and provided care in a residence for seniors. In addition, he has helped other provider groups develop house-call practices and has collaborated on research on home care.

Ratner was recently honored for his

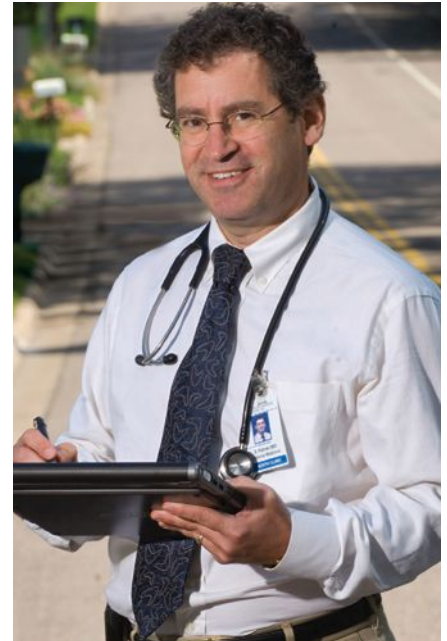


Photo by Steve Wewerka

Ed Ratner, M.D., has brought much-needed attention to end-of-life care.

work. Last month, he received the University of Minnesota's Outstanding Community Service Award, which recognizes members of the university community who make substantial, enduring contributions to the community and society.

Although Ratner appreciates such attention, he is even more pleased that his efforts are having an impact. For the first time in 2009, more Minnesotans died in their homes than in hospitals, according to the Minnesota Department of Health.

At a Glance

Name: Ed Ratner, M.D.

Specialty: Geriatric medicine

Practice: House Call Specialists, a private practice in the Twin Cities, and part-time faculty at the University of Minnesota Medical School

Medical training: University of Chicago Medical School, 1982; residency, Michael Reese Hospital, Chicago, 1985; fellowship, University of Minnesota, 1987-1990

MMA involvement: Member of the MMA's Ethics Committee and chair of the Provider Orders for Life Sustaining Treatment (POLST) work group organized by the MMA

The New Transplant Patient

| By Kate Ledger

Older, sicker patients are becoming eligible for organ transplantation, increasing the need for organs and raising new questions about who should get priority on waiting lists.



Illustration by Andree Tracey

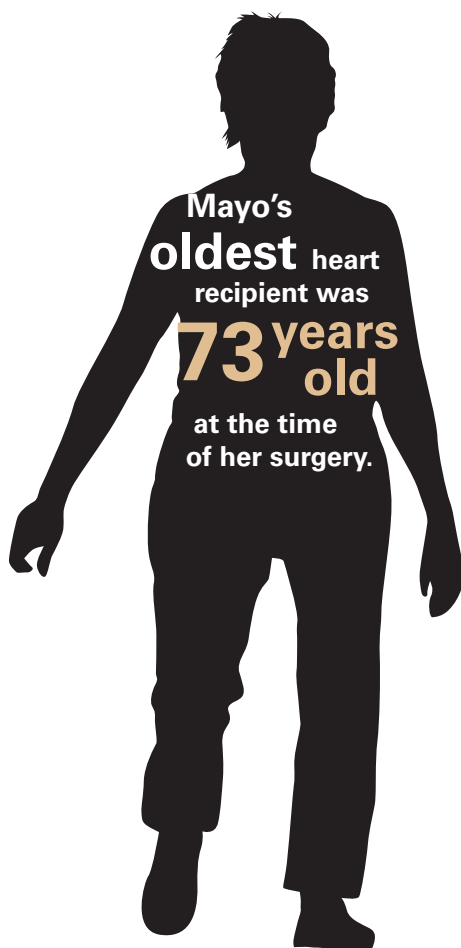
Ardell Lien of Caledonia, Minnesota, had a history of heart trouble that started with atrial fibrillation when he was in his 30s; but nothing prepared him for the devastation of congestive heart failure that hit hard a few decades later. The golf-playing, globetrotting father of three, who'd once lived on a boat with his wife, Maureen, could barely walk or take a shower without experiencing extreme fatigue by the time he'd reached his 60s.

Lien's family and friends encouraged him to go to Mayo Clinic for further evaluation, and there, Lien was surprised to learn that hope still existed. His doctor, Brooks Edwards, M.D., thought Lien would be a good candidate for a heart transplant. "I never thought I'd be eligible for that kind of surgery at age 67," Lien says. What's more, Lien remained a candidate even as his kidneys began to fail while he was waiting for a new heart.

As his health rapidly withered, Lien was moved to tears when he learned that a heart and a kidney had suddenly become available. In January 2003, he underwent a 12-hour double-organ transplant. His recovery astounded his family. Within months, he was reroofing his house. Two years later, at age 69, eager to acknowledge the measures that had saved his life, he embarked on a highly publicized solo trip around the world by 27-foot sailboat. The amazing feat (only a handful of individuals have ever circumnavigated the globe on their own, and Lien was the first transplant recipient to undertake the arduous journey) enabled him to raise awareness about advances in organ transplantation and the impact of organ donation, as he met with doctors and patient groups at ports around the world.

Now 76 years old and in continuing good health, Lien represents a trend: A growing number of people in their 60s and 70s are eligible for organ transplants. Sicker patients are finding their way onto the waiting list for organs, too.

The ability to perform transplants on such patients is the result of several factors including advances in drugs



for immunosuppression and more refined tissue-matching technology. What's more, as medications for treating chronic diseases have improved, even patients with conditions such as HIV and hepatitis C now may be eligible to receive a donated organ. Although these developments have given a second chance to some patients facing organ failure, they've also lengthened the list of people waiting for an organ. "The real limitation we face," says Timothy Pruett, M.D., chair of the division of transplantation at the University of Minnesota, "is having enough organs."

Transplantation Comes of Age

Although organ transplantation may once have been considered an extreme or even experimental treatment, it's taken its place during the last two decades as a mainstream therapy for organ failure. In patients with kidney failure, for instance, it's been shown to provide better outcomes

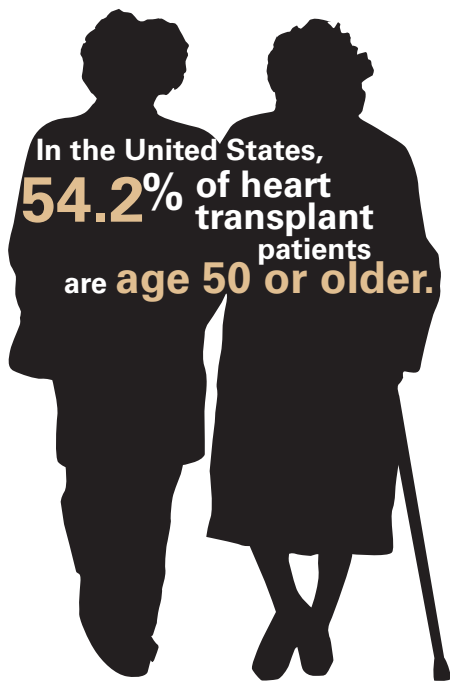
than dialysis. Consequently, transplants are being offered to more patients today than 10 years ago.

One reason why transplant medicine has been able to make such strides—and why it has become an option for people like Lien who may once have been ineligible—is the introduction of powerful anti-rejection drugs. A significant milestone took place in 1983 when the immunosuppression drug cyclosporine came on the scene, dramatically reducing organ-rejection rates. Cyclosporine and tacrolimus, which was introduced about a decade later, also enabled patients to minimize or avoid steroid treatment after receiving a transplanted organ, reducing subsequent infections and other complications. A handful of other antirejection drugs have since been introduced that allow more specific suppression of the patient's immune system and cause even fewer side effects. "In the past, as we were giving more broad-spectrum bone marrow suppression to patients, we'd have problems with postsurgical healing. That would limit the type of patient that could withstand surgery," explains University of Minnesota transplant surgeon Ty Dunn, M.D., who specializes in the treatment of complex patients.

Another milestone was reached in 1994, with the introduction of antiviral medication that reduced postoperative infections. Used in combination with antirejection drugs, the antivirals helped make positive outcomes much more common. "We were able to confidently offer transplants to patients who were a little bit older and a little frailer," Dunn says.

In fact, these developments prompted institutions that had set age limits for transplant patients to rethink them. Back in 1983, Mayo had determined that the cutoff for being eligible for a heart transplant would be age 65, recalls Edwards. But over the next decade, that number began to look arbitrary. For one thing, it became clear that individual patients age differently and that some older patients were fit for surgery.

In 1993, Mayo removed the age restriction, allowing patients to be considered based on their overall health. Edwards



says that if patients maintain muscle mass and bone density, and have excellent liver function and cognitive abilities, Mayo will consider them. “We look more at the physiological age than calendar age,” he says, adding that they probably unfairly excluded some patients in the past because of how old they were. (To date, Mayo’s oldest heart recipient was 73 years old at the time of her surgery, and she’s still going strong six years later at 79.)

Overall, Edwards says, the outcomes for heart transplant patients show that removing the age limit has been reasonable: Mayo’s three-year survival rate for patients younger than 60 is 87 percent; for patients older than 60, it’s 86 percent. What’s been critical, he adds, is that physicians have developed a keener sense over the years of proper patient selection: “We’ve gotten better at selecting patients who have the right stuff, who can withstand the challenges of a big procedure and the commitment to the rehabilitation that comes after it.” In addition, physicians have discovered that older patients, whose immune systems are less robust than younger ones, tend to accept organs better.

A Series of Medical Advances

Over the years, surgical advances have enabled sicker patients to be added to the

waiting list for organs as well. Patients with heart failure, for instance, often have problems in other organs such as the kidneys. When Mayo established its transplant center in 1999, it put transplant surgeons and physicians who specialize in disparate organ systems in close proximity to learn from one another. As they gained experience, they began conducting multiple-organ transplants. “We’ve probably performed more combined transplants than anywhere in the country,” Edwards says, noting the center has performed 107 simultaneous liver-kidney transplants, 21 heart-kidney, 21 heart-liver, and one heart-liver-lung transplant.

In fact, combined transplants have been an incredible boon for medically complex, high-risk diabetes patients, points out Dunn. Although they were once excluded from receiving new kidneys because transplant results were so bad, patients with diabetes who receive a combined kidney-pancreas transplant, or a kidney first and a pancreas at a later date, can be free from dialysis and also from diabetes. “That’s a huge advantage when you’re talking about going on life-long immunosuppression,” Dunn says. “Ideally, you don’t want to be diabetic and at risk for infections from immunosuppression at the same time.” She says the university has been doing kidney-pancreas transplants since 1967 and that the outcomes keep getting better. The university has research protocols underway in which diabetic patients with kidney failure can receive a kidney and then a transplant of insulin-producing islet cells to restore the pancreas function they’ve lost.

Some of the most difficult patients to transplant are those who already have antibodies in their system. They’re known as “sensitized” patients, and they have been exposed to foreign human antigens through blood transfusions, previous transplants, or pregnancy and developed the antibodies to them. These antibodies are present in about 30 percent of patients and can present a significant challenge when it comes to finding a compatible donor.

But advances in the last five years

have enabled doctors to detect antibody levels much more precisely. In the past, predicting donor compatibility involved some degree of guesswork and the rare-but-catastrophic problem of hyperacute rejection, where within minutes of blood flowing into the new kidney, a patient would mount a rejection response and the organ would fail, was a concern. “It’s so rare now,” Dunn says, “that most of the people who have been trained in the last decade have never even seen hyperacute rejection. Our tissue-typing practices are much more sensitive and specific than ever before. You can actually put names on the different tissue antigens and plan ahead to avoid them when considering a donor.”

And there are now protocols available to help patients who have problematic levels of antibodies. Dunn uses one of several desensitization techniques that can make these patients—an estimated 5 percent of those for whom transplant would have once been impossible—eligible for a new organ. One technique involves giving a sensitized patient high-dose intravenous immunoglobulin (IVIG) to dampen the activity of B cells that produce antibodies. In another, called plasmapheresis, the patient’s blood is removed in order to “wash” away the problematic antibodies, then returned. In addition, antibody-depleting medications are now available. “We deploy these desensitization strategies on a very selective basis,” Dunn notes. “Our bodies have entrenched immune memory responses, and we can’t always predict how effective or durable the desensitization treatment will be.”

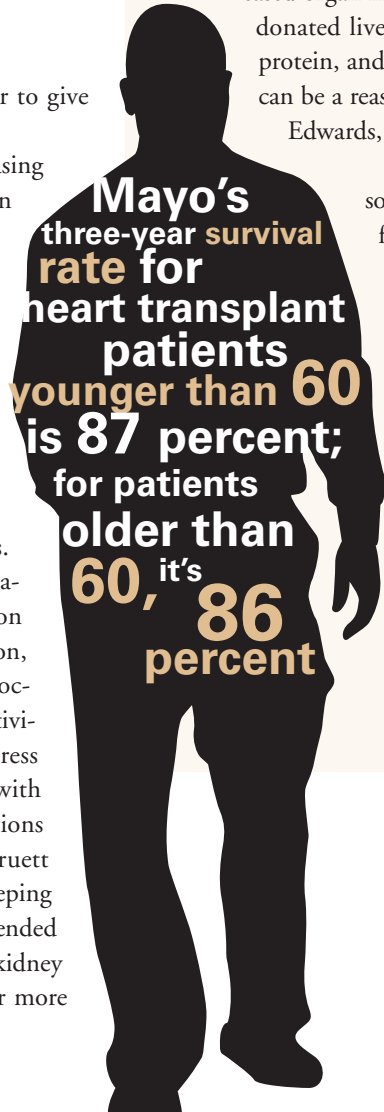
One area that is evolving is transplantation in patients with chronic viral infections. “It used to be that one of the huge contraindications for transplantation was being HIV-positive,” Pruetz says. “It turns out that with current antiviral drugs, people who have HIV under good control can do well with a transplant.” An article in the *New England Journal of Medicine* last year highlighted the success of kidney transplants in HIV-positive patients. Recently, federal health officials began pushing for the repeal of the ban on transplant-

“We’ve gotten better at selecting patients who have the right stuff, who can withstand the challenges of a big procedure.”

—Brooks Edwards, M.D.

ing HIV-positive organs in order to give them to HIV-positive recipients.

Pruett is interested in increasing access to kidney transplantation for people with hepatitis C, who represent between 5 and 10 percent of the population on dialysis. “They’re perceived as being folks who are at higher risk, and it’s clear—only about 1 percent of the people we transplant are hep C positive—they aren’t accessing transplantation as much as might benefit them,” he says. But over the last several years, hepatitis C has been the most common indication for liver transplantation, and through these transplants, doctors have learned more about antiviral drug therapies that can suppress the presence of the virus along with the immunosuppression medications that stave off organ rejection. Pruet believes that knowledge about keeping the viral load in check can be extended to hepatitis C patients who need kidney transplants: “I think we can offer more



**Mayo's
three-year survival
rate for
heart transplant
patients
younger than 60
is 87 percent;
for patients
older than
60, it's
86
percent**

A Question of Supply

Numerous campaigns over the last decade have highlighted organ donation in an attempt to increase the number of people identified as potential donors.

Because some of the latest research has shown, particularly in the case of kidney patients, that organs from living donors work even better than those from deceased ones, the push is on to raise awareness about the opportunity—and benefit—of giving a kidney to someone in need. Because not all donors who want to give a kidney to a sick friend or relative are compatible, one of the recent advances in kidney donation is “paired donation,” in which a donor who’s not compatible with the person to whom they wish to give their organ can give the organ to another patient whose donor will, in turn, provide a more compatible organ. More than 260 kidneys have been exchanged in such arrangements. The concept has been so successful that the United Network for Organ Sharing is about to roll out a national campaign for paired donation, hoping to increase awareness of this life-saving option.

Another strategy to increase the number of living donors is the use of “domino” transplants, in which one patient’s diseased organ is given to another patient who can make use of it. For instance, a 50-year-old with familial amyloidosis, a disease in which the liver produces abnormal proteins that accumulate over time and damage other organs, may require a new liver. But the diseased organ may still be usable for a 60-year-old with liver failure. “The donated liver itself will work fine, except for making that abnormal protein, and since it takes decades for that protein to cause damage, it can be a reasonable organ for an older patient to receive,” says Brooks Edwards, M.D., director of Mayo Clinic’s Transplant Center.

Arthur Matas, M.D., director of the University of Minnesota’s renal transplantation program, has posed another idea for increasing the pool of available organs: providing compensation to donors. He believes this may be a reasonable way to make organ donation more compelling and has been speaking about it for several years. Currently in the United States, it’s illegal to provide any compensation for a donated organ. He points out that sperm, plasma, and egg donations do involve payment, “so there’s precedent.” He adds that such a system would have to involve government oversight. But it’s an issue that remains hotly debated. Among concerns about compensation is the disparity between rich recipients who can afford the transplant and impoverished donors. “People get very passionate about the topic,” Matas notes, “on both sides.”—K.L.

transplants for people with hep C than we currently do.”

More Patients Need More Organs

The fact that more patients are candidates for organ transplantation means that more organs than ever before are needed to meet the demands. The United Network for Organ Sharing (UNOS), the private, nonprofit organization contracted since 1984 by the federal government to keep a list of potential recipients, has more than 110,000 people on its waiting list for an organ (72,000 of them are considered “active,” meaning they would be physically ready if an organ became available and don’t have another medical complication such as cancer that must be resolved first). The list grows by more than 4,000 patients a month. Delineated regions within the United States maintain their own lists of patients needing organs. (The Upper Midwest region, which includes Minnesota, North and South Dakota, and three counties in Wisconsin, has 2,300 patients on its list. That number increases slightly each year.)

In renal transplantation, the largest area of transplantation with nearly 20,000 surgeries a year, growing demand for kidneys has not only expanded the waiting list but also broadened the types of organs that are deemed usable. Arthur Matas, M.D., director of the University of Minnesota’s renal program, has seen that trend firsthand. “When I saw patients here in 1980, I would tell a patient that if they went on the list for a deceased organ transplant, they’d wait a year—and add to that, we’d only use kidneys from young trauma victims. Now I tell patients they’re going to wait five years and not only do we use kidneys from young trauma patients but we use kidneys from older people who died of strokes. We’re using kidneys we wouldn’t have used back then just because the need has gotten so much greater.”

But even as more people become candidates for transplantation, the fact is for the majority on the waiting list, compatible organs do not materialize in time. Most wait more than five years, and annu-

“Transplantation is a treatment that has built-in limits because we don’t have enough organs for everybody.”

— Barbara Koenig, Ph.D.

ally more than 6,000 people die waiting for a transplant. “For those of us in the field, that’s devastating,” Pruettt says.

Ethical Quandaries

As the field of transplantation continues to evolve, along with strategies that make it possible to transplant organs into older and sicker patients, thorny ethical issues are emerging. “Unlike other life-saving medical interventions, transplantation is a treatment that has built-in limits because we don’t have enough organs for everybody,” notes Mayo bioethicist Barbara Koenig, Ph.D. Those limits have prompted many to wonder whether older and sicker patients even belong on the waiting list for organs.

A recent proposal by UNOS would replace the current kidney allocation system, in which patients receive priority based on the length of time they have been waiting, with one that would more concertedly match younger, healthier organs to younger patients. The idea is to direct the organ to where it will have the best possible chance of functioning the longest.

Some bioethicists have argued that the only way to address the need for hearts, for instance, given the limited supply available, is to decrease demand and make the selection criteria for candidates more stringent. Koenig puts it this way: “It’s not feasible for our society that everybody can have four heart transplants before they die. We need to balance competing goods—helping individuals live longer with concerns about social justice.”

One of the domains that needs to be

addressed from a bioethics and a policy standpoint is the increasing age of organ recipients. “Is it reasonable for an older person to have a 20-year-old’s organ that comes available in an accident? Or to ask a 20-year-old to donate a kidney to a parent or grandparent?” Koenig asks. “What is the upper cut-off, and are we going to have one?” She predicts the ongoing tension will increase between the push to do more medically, to do more transplants for higher-risk and older patients, and the consequences of not having enough organs.

But even as the nation sets policy about the allocation of organs, each institution will have to navigate on its own what is medically possible for patients amid parameters that are constantly shifting. “People want everyone to be treated well,” Pruettt says. “We’ve learned, for example, that transplantation offers an optimal kind of treatment to help patients live longer. A kidney transplant is cheaper, on a national scale, than dialysis. And a transplant can provide a high quality of life. But we can’t do it for everybody. We just don’t have the resources to do that. So the question becomes, how do we do the best with what we have, and how do we draw boundaries? The answer is that the questions are still evolving, and no one knows for sure right now.”

MM

Kate Ledger is a St. Paul freelance writer and frequent contributor to *Minnesota Medicine*.

Minnesota **Firsts**

A timeline of transplant milestones.

Minnesota has been a leader in transplant medicine since the 1960s, pioneering and refining techniques for pancreas transplantation, bone marrow transplantation, and islet cell transplantation, and training many of the surgeons who have gone on to make their mark at institutions around the world. The following timeline highlights a few of the “firsts” that occurred in the state and the people behind them, as well as some of the events that have been turning points in organ transplantation in this country.



The University of Minnesota's David E.R. Sutherland, M.D., Ph.D.

1963

University of Minnesota and Mayo Clinic establish organ transplantation programs. Surgeons from both facilities perform kidney transplants.

1977

David Sutherland and John Najarian perform the world's first islet autograft transplant on a person with pancreatitis.

1966

University of Minnesota surgeons Richard C. Lillehei, M.D., and William D. Kelly, M.D., perform the world's first pancreas transplant.

1974

University of Minnesota surgeons David E. R. Sutherland, M.D., Ph.D., and John Najarian, M.D., perform the first islet cell allograft transplant (from a deceased donor to a living recipient) to treat diabetes.

1967

Richard Lillehei and William Kelly perform the world's first simultaneous pancreas-kidney transplant. That same year, Lillehei and his team perform the first reported small bowel transplant.

1972

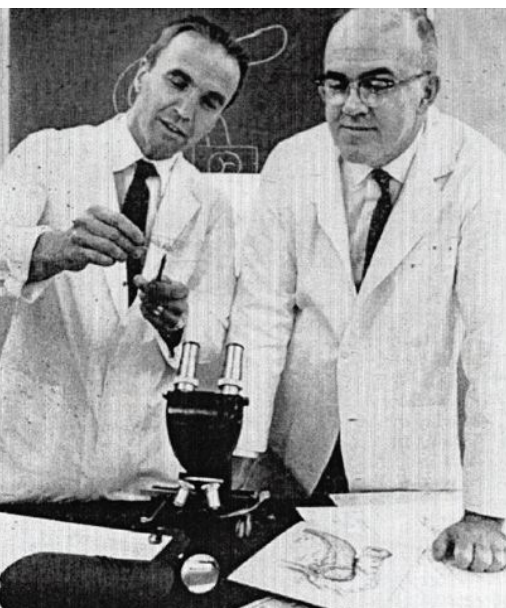


Passage of the End Stage Renal Disease Act paves the way for Medicare coverage of renal dialysis and kidney transplants.

1968

The University of Minnesota's Robert Good, M.D., performs the first successful bone marrow transplant on a 4-month-old boy with severe combined immunodeficiency syndrome. He uses bone marrow from the boy's sister.

The Uniform Anatomical Gift Act establishes the first national organ and tissue donation policy in the United States. The first U.S. organ-donor programs are established.



Transplant pioneers Richard C. Lillehei, M.D., and William D. Kelly, M.D.



The University of Minnesota team that led a number of history-making transplants, pictured in 1980. They are (standing from left) Ronald Ferguson, M.D., Ph.D., John Najarian, M.D., and David Sutherland, M.D., Ph.D. Seated (from left) are Richard Simmons, M.D., and William Payne, M.D.

David Sutherland performs the world's first partial pancreas transplant from a living related donor.

1979



John Najarian, M.D., with Jamie Fiske, who received a liver transplant in 1982 at 11 months of age.

1982

John Najarian performs a liver transplant on 11-month-old Jamie Fiske after her parents launched a national campaign to find her an organ. Her story led to the passage of the National Organ Transplant Act in 1984, which called for a single national network for allocating organs.

1983

The FDA approves the immunosuppressant drug cyclosporine. Cyclosporine transforms organ transplantation from an experimental procedure to a routine one.

1984

U.S. Congress passes the National Organ Transplant Act, which establishes the Organ Procurement and Transplantation Network to maintain a national registry for organ matching. The law calls for the network to be run by a nonprofit. The United Network for Organ Sharing is given the contract and proceeds to develop the organ allocation system in the United States.

David Sutherland performs the first unrelated living-donor pancreas transplant. That same year, Sutherland and Paul Gores, M.D., conduct one of the world's first clinical islet transplant trials using single donors of simultaneous kidney transplants.

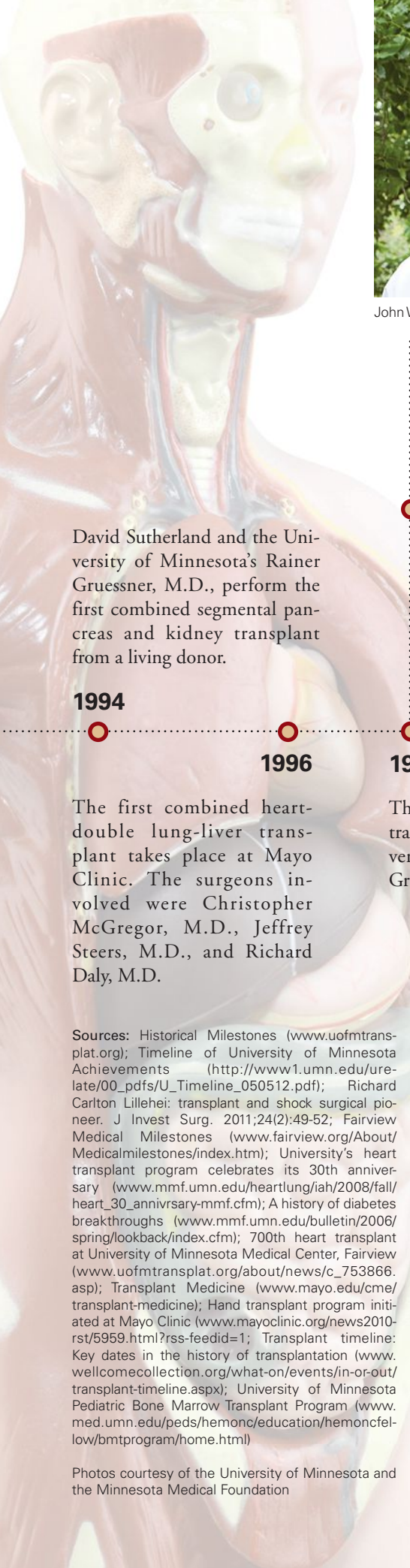
1992

1987

A University of Minnesota/Mayo Clinic collaborative led by David Sutherland and James D. Perkins, M.D., results in development of a technique for simultaneous liver/pancreas procurement.

The National Marrow Donor Program is founded and headquartered in the Twin Cities.





John Wagner, M.D.

The University of Minnesota does its 5,000th bone marrow transplant.

John Wagner, M.D., leads a team that performs the world's first bone marrow and cord blood transplant to treat recessive dystrophic epidermolysis bullosa at the University of Minnesota Amplatz Children's Hospital.

2007

2004

Surgeons at the University of Minnesota Medical Center, Fairview, perform the university's 6,000th kidney transplant.

2000

Rainer Gruessner, David Sutherland, and Raja Kandaswamy, M.D., perform the first simultaneous laparoscopic living donor pancreas-kidney transplant.

2010

The University of Minnesota performs its 700th heart transplant since its program began in 1978. Ranjit John, M.D., Kenneth Liao, M.D., and Cindy Martin, M.D., lead the team.

Mayo Clinic establishes the first clinical hand transplant program in the United States.

David Sutherland and the University of Minnesota's Rainer Gruessner, M.D., perform the first combined segmental pancreas and kidney transplant from a living donor.

1994

The first combined heart-double lung-liver transplant takes place at Mayo Clinic. The surgeons involved were Christopher McGregor, M.D., Jeffrey Steers, M.D., and Richard Daly, M.D.

1996

1997

The world's first kidney-bowel transplant is done by the University of Minnesota's Rainer Gruessner.

Sources: Historical Milestones (www.uofmtransplat.org); Timeline of University of Minnesota Achievements (http://www1.umn.edu/urelate/00_pdfs/U_Timeline_050512.pdf); Richard Carlton Lillehei: transplant and shock surgical pioneer. *J Invest Surg.* 2011;24(2):49-52; Fairview Medical Milestones (www.fairview.org/About/Medicalmilestones/index.htm); University's heart transplant program celebrates its 30th anniversary (www.mmf.umn.edu/heartlung/iah/2008/fall/heart_30_annivrsary-mmfcfm); A history of diabetes breakthroughs (www.mmf.umn.edu/bulletin/2006/spring/lookback/index.cfm); 700th heart transplant at University of Minnesota Medical Center, Fairview (www.uofmtransplat.org/about/news/c_753866.asp); Transplant Medicine (www.mayo.edu/cme/transplant-medicine); Hand transplant program initiated at Mayo Clinic (www.mayoclinic.org/news2010-rst/5959.html?rss-feedid=1); Transplant timeline: Key dates in the history of transplantation (www.wellcomecollection.org/what-on/events/in-or-out/transplant-timeline.aspx); University of Minnesota Pediatric Bone Marrow Transplant Program (www.med.umn.edu/peds/hemonc/education/hemonc-fellow/bmtprogram/home.html)

Photos courtesy of the University of Minnesota and the Minnesota Medical Foundation



The team that led the 700th heart transplant at the University of Minnesota Medical Center, Fairview in 2010: (from left) Ranjit John, M.D., Cindy Martin, M.D., and Kenneth Liao, M.D., Ph.D.

The First and Last Days of Medicine

By Maura Scanlon

On a busy morning, a doctor stops to ask what a patient really wants—and finds out it isn't more treatment.

Day 1 of Med 1 morning rounds. I tentatively follow a long train of white coats down the hallway toward Shirley E's room. As our Firm D team approaches, her low-pitched moans and high-pitched wails forewarn us of the rollercoaster that lies ahead. We find Shirley, a robust woman, with her gowns and draping strewn about her bare yellow body, which is thrashing. Her 30-something daughters stand in the corner of her room, embarrassed and defeated by their mother's illness.

Following Dr. M's lead, we attempt to calm and redress her, and bandage her IJ port while asking about her favorite foods, her children, and other things. Although unable to identify time or place, Shirley's encephalopathic mind quickly recognizes our poorly camouflaged attempts at distraction as an insult to her personhood.

She won't have it.

I couldn't believe this was my first patient on my medicine rotation, and I feared the next one. Shirley was nothing like the pediatric patients I had seen on my previous rotation or the painfully polite actors playing patients in our Physician and Patient class. That morning, we saw a fair number of patients with altered mental status. However, none were like Shirley.

As the days and weeks passed, no other patient proved to be as informative, comical, emotional, and real.

I quickly realized that through Shirley, I was learning not only about the art of diuretic and lactulose titrations but also about how quickly hope blossoms with the subtlest signs of improvement and how quickly it can fade.

We were encouraged as Shirley progressed from knowing which country she was living in to knowing the name of the

Shirley told us about her nightly hallucinations—a white curtain floating, hanging over her bed, turning into a spooky black drape.

hospital she was in and on which side of the Mississippi River it was located. As her chronic liver failure was managed over the next two weeks, she seemed to improve and almost become well. We grew close as we celebrated her simple joys. Her daughters began to refer to Dr. M as “part of the family.” On the day of her discharge, I walked into her room to find her sitting upright in the chair beside her bed eating Cheerios. “Just a dabble of milk and sugar, just right,” she said with a yellow, toothy grin.

We thought she was a true success story, a patient who had recovered from a flare of nonalcoholic steatohepatitis (NASH), and who had several good years of life yet to live.

To our surprise, Shirley returned to us a few days later much altered—puffy and in distress. The CT scan of her psoas abscess upon discharge likely had induced contrast-nephropathy—acute renal failure, on top of her NASH. This time, it was not only her edematous and jaundiced body that ailed but also her spirits.

“Why did this happen?” she asked. Along with our new attending and the resident team, we tried to explain that this turn of events was just how her body was reacting. We tried to tell her that we were still hopeful for a liver transplant and gradual resolution of her newly developed acute tubular necrosis.

One morning Shirley told us about her nightly hallucinations—a white curtain floating, hanging over her bed, turning into a spooky black drape. Her dreams seemed strikingly symbolic of her disease and her mood, as one day she was improving and cheerful and the next she was on dialysis, feeling hopeless.

Over the course of three more weeks, Shirley’s determination and will to live slowly faded. Yet as her spirits sagged

and her abdomen swelled, her witty mind stayed clear. One day, a resident made the mistake of entering her room with a Coke. She joked that since she was fluid-restricted, *no one* should be allowed to drink in her room. Every morning after that, as we circled her bed, her eyes would dart around the room to make sure no one had a beverage.

During morning rounds on the last day of my medicine rotation, Shirley asked me a startling question: Is it worth it?

She wondered how the dialysis port and peg tube that had been inserted were going to affect her life. I was initially taken aback. But as I thought about it, I had no doubt that every single one of the doctors, nurses, and others taking care of her had silently wondered this. Yet we had all assumed Shirley wanted this care, even though she never explicitly told us she did. As it turns out, at a care conference earlier in the week, Shirley’s family, not Shirley, had decided to move forward with the dialysis, peg tube, and transplant listing.

On the final day of my rotation, Dr. M, like an angel sent back to our service seemingly just for this patient, crouched next to Shirley at her bedside. With a soothing but strong voice, Dr. M explained at length that the decision whether to be treated was hers—not ours, not her family’s. He said we could continue to treat

her, hoping that her kidneys would return to function and that a liver would become available. Or, we could simply stop it all, make her comfortable, and let her die in peace.

It then began to unfold. Shirley was tired and not interested in undergoing dialysis three times a week; she did not really want a new liver or a life on transplant medications. She was exhausted, but content. She was ready to meet her creator.

In the moment when Dr. M crouched beside her bed, I discovered how important it is to get down on the patient’s level and discuss the important issues that are all too often swept aside. Dr. M presented the arguments for continuing treatment and for palliative care. As it turned out, Shirley was at peace with the idea of dying.

On the last day of medicine, one of the most poignant lessons on patient care gently revealed itself in a quiet voice. I could have missed it. Although sad, it was a tender moment as Shirley’s voice was finally heard.

It was a bittersweet end to our morning rounds and my medicine rotation. While trailing behind white coats on morning rounds, in a busy hospital, on Firm D, we learned about confronting mortality at the bedside. **MM**

Maura Scanlon is a third-year medical student at the University of Minnesota.

Stem Cell Research in Minnesota Here Today, Gone Tomorrow?

A bill moving through the Legislature threatens to disrupt progress on therapies that are already helping patients.

By Meri Firpo, Ph.D., and John Wagner, M.D.

Medical research that could help Minnesotans living with devastating diseases is being threatened by a bill working its way through the Minnesota Legislature. If passed, it would stifle innovation and criminalize research that could transform the way we treat disease.

On the surface, the bill (H.F. 998/S.F. 695), sponsored by Rep. Bob Dettmer, R-Forest Lake, and Sen. Michelle Fischbach, R-Paynesville, proposes banning reproductive cloning—that is, outlawing science that culminates in the creation of a human that is a replica of another. Banning human reproductive cloning is a move that every reputable biomedical scientist would wholeheartedly support. But proponents of the bill have admitted publicly at hearings in St. Paul that this legislation attempts not only to prevent human reproductive cloning but also to ban somatic cell nuclear transfer (SCNT), which has been referred to in the lay press as “therapeutic cloning,” and restrict embryonic stem cell research.

What is particularly concerning is that the proponents of the bill are acting without an accurate understanding of the science behind SCNT or the support of an informed public. SCNT is a laboratory technique that involves the transfer of a cell nucleus from a somatic cell into an enucleated egg (one from which the nucleus has been removed). The technique produces a formless group of cells that is smaller than the cross-section of a human hair. The bill’s supporters argue that SCNT could lead to the creation of a baby. This is not feasible because cells created through SCNT cannot survive for long in culture (they survive only long enough for extraction of their inner mass, from which a new cell line can be derived). Yet SCNT does have the potential to save lives, rejuvenate the biomedical industry in Minnesota, and change the practice of medicine as we know it.

..... **Treating Disease**

One of the areas most likely to benefit from SCNT for therapeutic purposes is tissue transplantation. We work at a university that is world-renowned for its success both in solid-organ and blood and marrow transplantation. We have been a leader in these areas since the 1960s. And while we have made great strides, there is more work to be done, particularly related to the problem of graft rejection. Today, all patients who undergo solid-organ and many who have cellular transplants such as islets are required to remain on lifelong immunosuppression to prevent rejection. Some reject their organ; and others suffer the toxic side effects of antirejection medicine resulting in life-threatening complications such as kidney and liver failure or opportunistic infections.

One strategy for obviating the need for lifelong immunosuppression is to transplant patients with cells or tissue that have been created through SCNT. Using SCNT, researchers would remove the genetic material from an unfertilized egg cell, then introduce the nucleus of a mature cell from the patient, such as a skin cell, into the enucleated egg cell. The resulting cells that would develop would acquire the surface antigens that are encoded in the patient’s genes, making it a perfect tissue match. Although it is being done elsewhere, SCNT is not currently being done at the University of Minnesota because of state funding restrictions; but it could be an important research tool in the future.

Being able to create tissue or cells for transplant would not only allow us to overcome the complications of immunosuppression but also make the transplant process less expensive and more accessible, as patients would not have to wait for organs to become available.

Those opposed to all uses of SCNT have made much of

the possibility of using induced pluripotent stem (iPS) cells in research and for therapies. These stem cells are created by taking an adult cell, such as a skin cell, and introducing genes that reprogram it into an embryonic stem cell state. As with SCNT, this process results in a matched cell line for the patient. This technology holds promise, as it enables researchers to create pluripotent stem cells from adult stem cells. We are working with these cells at the university, trying to come up with a supply suitable for transplantation in people with type 1 diabetes, Hurler syndrome, Fanconi anemia, and other diseases. But we don't yet know whether the tissues created in this way will be safe for transplant into human patients. If they are not, and if SCNT is criminalized, we will have no other option for making patient-specific cells.

In addition, using cells produced through SCNT is the only way to treat specific neurological disorders caused by defects in the mitochondria such as Leber's hereditary optic neuropathy and myoclonic epilepsy with ragged red fibers. Adult cell reprogramming (iPS) is not an option because the process does not eliminate the diseased mitochondria.

..... **Separating Fact from Fiction**

Our legislators do not need to know every detail about SCNT. However, they do need to understand that it is not human cloning and that it is very important to research that is leading to new therapies. And before they set legislative limits, they need to be aware of a number of facts.

1. The intent of research involving SCNT is to save lives and improve health. Beyond the ethics of replicating an individual, there is another reason why there is broad scientific consensus for not using SCNT for reproductive purposes. We know from animal cloning research, such as the work that resulted in the birth of Dolly the sheep, that severe birth defects and risks to the mother are common consequences of reproductive cloning. Supporters of the bill present a science fiction view of this technology as a scare tactic, and their view is based on a misunderstanding of the intent of medical research. Furthermore, there is considerable oversight in place at the federal and local levels that ensures that the research we do is ethically sound and appropriate.
2. It would be premature and foolish to limit ourselves to the study of adult stem cells. Although there is substantial interest in figuring out how to make adult stem cells into useful therapies, today they are used to repair only one tissue—bone marrow.
3. It is true that embryonic stem cells have not cured a single disease—and for good reason. The severe funding restrictions put in place under the Bush administration along with other local restrictions have severely limited research with embryonic stem cells. In the past six months, however, trials using embryonic stem cells elsewhere in the country have opened for spinal cord injuries, Stargardt disease (a progressive disease that leads to blindness in young people), and macular degeneration. It is unlikely that similar trials would

ever be offered in this state if this kind of restrictive legislation passes.

4. The pre-eminent leaders in stem cell science all recognize the importance of embryonic stem cell research, including that involving SCNT. Some of our state legislators, however, have argued that stem cell researchers have given up on the need for patient-specific embryonic stem cells derived by SCNT, citing remarks taken out of context from Professor Ian Wilmut, who cloned Dolly the sheep, and Professor Rudolf Jaenisch, who first used SCNT in studying immunodeficiency disease. The proponents of the bill never went to the primary sources—Wilmut and Jaenisch. We did. Although they are now involved in other areas of investigation, Wilmut and Jaenisch have never abandoned the need for SCNT for the reasons stated above.
5. The ability to reprogram adult cells (iPS cells) does not eliminate the need for SCNT. Reprogramming requires genetic manipulations, which means resultant cell lines are years away from clinical testing. We know substantial hurdles need to be overcome before these cells can be used in any treatment, and we have shared that fact with Food and Drug Administration officials. Furthermore, it is yet to be proved that iPS cells have the full potential of embryonic stem cells. Interestingly, SCNT and the cell lines derived through that process are needed to help us understand how to make adult cells “embryonic-like.”

..... **Limiting Research Limits Discovery**

Lawmakers and the public need to understand there will be serious consequences for patients, medical researchers, and the state's economy if this bill becomes law. Patients with incurable diseases will be cut off from future treatments developed anywhere—as it will become a crime even for patients who have had such treatments to return to Minnesota. (Language in the bill suggests a person cannot bring cells back into the state, and this could be interpreted to include cells that are in the body.) Minnesota will lose its standing as a leader in the biomedical field because companies will be limited in what they can produce. And some of the state's most promising researchers will move to places with policies that are more welcoming.

From its inception, the University of Minnesota's Stem Cell Institute has been interested in pursuing research on many types of stem cells—from adult stem cells, to embryonic stem cells, to the newest potential source—iPS cells. To cut off an area of related research now would be shortsighted. We should not let science and medicine be driven by a vocal minority. We must continue to be a state that welcomes scientific innovation and creativity. **MM**

Meri Firpo is assistant professor of medicine and a member of the Stem Cell Institute, and John Wagner is professor of pediatrics, director of the division of blood and marrow transplantation, and scientific director of clinical research of the Stem Cell Institute at the University of Minnesota.

Paying for End-Stage Renal Disease Treatment

EDITOR'S NOTE: Treatment for end-stage renal disease (ESRD) in the United States cost \$39.5 billion in 2008. Most of that expense—\$26.8 billion—was covered by the federal government, which pays for dialysis or kidney transplantation for nearly all Americans through the Medicare program. These articles, which first appeared in the February 17, 2011, issue of the *New England Journal of Medicine*, describe how the government came to be the largest payer for treatment of ESRD and how it is testing a new payment model aimed at holding down costs.

Special Treatment—The Story of Medicare's ESRD Entitlement

How coverage for one specific disease came to be.

By Richard A. Rettig, Ph.D.

On October 1972, Medicare, which had been enacted for the elderly in 1965, was extended to the disabled by the Social Security Amendments. One provision, added at the last minute, declared that persons with chronic renal disease who required hemodialysis or kidney transplantation “shall be deemed to be disabled” for purposes of Medicare Parts A and B. To be eligible for this Medicare coverage, patients had to have paid into the system long enough to be “fully or currently insured” under Social Security or be the spouse or dependent child of someone who was. This near-universal Medicare entitlement for end-stage renal disease (ESRD) has now been in effect for nearly 40 years.

The consequences in numbers of beneficiaries and in expenditures have been significant. In 2008, there were more than 112,000 new patients with ESRD in all eligibility categories (elderly, disabled, and ESRD-only). There were approximately 548,000 U.S. patients undergoing dialysis at the end of 2008, but many of them were not covered by Medicare, either

because they had not yet fulfilled the initial waiting period or because they had received transplants and their coverage had ceased after three years. Medicare expenditures for ESRD in 2008 were \$26.8 billion for Parts A and B. Non-Medicare expenditures for ESRD (covered by employer-sponsored group health plans or paid directly by patients) added another \$12.7 billion, for total national expenditures of \$39.5 billion.¹ According to an analysis by the U.S. Renal Data System, ESRD beneficiaries represented 1.3 percent of all Medicare beneficiaries and used 7.9 percent of Medicare expenditures.¹

So how was it that full coverage for treatment of one specific disease became enshrined in U.S. law? The story began during World War II, in Nazi-occupied Holland, where Willem Kolff invented the artificial kidney; after a visit by Kolff to the United States in 1947, a modified version of his machine was developed and used in Boston by John Merrill and colleagues at the Peter Bent Brigham Hospital. During the Korean War in the early 1950s, proof of concept was provided for treat-

ing acute renal failure with this Kolff-Brigham device. In 1960, Belding Scribner and Wayne Quinton, at the University of Washington Hospital in Seattle, invented an implanted arteriovenous shunt that made it possible for a patient to be connected to the machine repeatedly and ushered in the use of hemodialysis as a treatment for chronic renal failure. The shunt was later replaced by a subcutaneous fistula developed by the physicians Michael Brescia and James Cimino at the Bronx Veterans Administration (VA) Hospital.

In the 1960s, in addition to dialysis, kidney transplantation was emerging as a treatment for chronic renal failure. The two therapies interacted in both complementary and competitive ways, each following its own developmental pathway. Though initially greeted with skepticism by many in the medical establishment, these therapies had demonstrated their clinical effectiveness by the mid-1960s.

Both life-saving treatments were costly—beyond the means of most individuals—and not covered by insurance. In Seattle, in response to financial limitations, access to dialysis was restricted through explicit rationing carried out by an anonymous lay committee—an approach that was laid bare for the American public in a *Life* magazine article in November 1962.² Elsewhere, decisions limiting access to dialysis were tacitly incorporated into traditional medical decision making. Dialysis highlighted the tragic choices that had to be made when fundamental societal values encountered problems of scarcity.³

The issue was clearly understood by many. For example, James Shannon, director of the National Institutes of Health (NIH), wrote to the Surgeon General in 1962 about the “difficulties” created by Scribner’s success: lives could be saved, but at a high cost to individuals and the country. This understanding permeated all policy discussions concerning how to respond. The recurrent issues were clinical effectiveness, patients’ rehabilitation and quality of life, and—central to everything—cost.

Advocates for a national treatment program pressed their case with Congress and the administration. The government responded. In 1963, the VA announced its intention to build dialysis centers in 30 VA hospitals throughout the country. The Public Health Service, beginning in 1964 and continuing through 1972, funded 12 dialysis centers, 12 home dialysis programs, and half a dozen organ-procurement efforts. The NIH, responding to congressional appropriations committees, established a contract research program within the National Institute of Arthritis and Metabolic Diseases to build a better, less costly dialysis machine; initiated a similar effort in transplant immunology within the National Institute of Allergy and Infectious Diseases; and nourished many important advances in kidney transplantation through the Clinical Research Centers program. Two registries—one for dialysis and one for transplantation—were supported by the NIH in building a database for epidemiology and policymaking.

A dilemma confronted policymakers. Only the VA had the legal authority to pay for direct patient care. The Public Health Service had authority only to support research, training, and

“demonstrations.” But once a patient began treatment, his or her need for care did not end at the conclusion of a time-limited grant or contract. The search for statutory authority to pay for direct patient care became a major element in the decade-long debate over what to do for Americans with ESRD.

In late 1965, the VA proposed a budget to the Bureau of the Budget to sustain the expansion of its dialysis centers program. Recognizing the broader national implications, the Budget Bureau, with help from the Office of Science and Technology, convened an expert committee to examine not only the VA effort but all federal government agencies involved with dialysis and kidney transplantation. Chaired by Carl Gottschalk, the committee included nephrologists, transplantation specialists, and economists. Its report, released in November 1967, recommended a national treatment program financed by amending the Medicare statute. It endorsed home dialysis over center dialysis, and transplantation over both, on the grounds of clinical effectiveness and reduced costs. But the Budget Bureau parked the report: financing the war in Vietnam had assumed priority over Great Society initiatives and had put a hard stop to all major new programs.

Home dialysis had developed as an alternative to center dialysis largely as a way of reducing costs and increasing access; the Gottschalk Committee report reinforced this development. By 1972, when the legislation was enacted, nearly 40 percent of all patients receiving dialysis, then numbering about 10,000, were receiving the treatment at home.

A Burgeoning Industry

The kidney-disease amendment to Medicare stemmed from the cumulative effect of demonstrations of clinical effectiveness, sustained advocacy, and previous incremental responses by the federal government. Many state governments also enacted programs to help patients with kidney failure during the same period. Consequently, there were steady increases in the numbers of dialysis and kidney transplantation centers, of newly minted nephrologists and transplantation specialists, nurses, and social workers to staff those centers, and of patients who were candidates for and recipients of the treatment they offered.

These facts were not lost on the news media: the *New York Times*, the *Wall Street Journal*, the *Washington Post*, NBC television, and local news outlets across the country brought the ESRD story to millions of Americans. Inevitably, these stories came to the attention of Congress and state legislatures.

In November 1971, a patient received dialysis—albeit very briefly—at a hearing of the House Committee on Ways and Means. Many casual observers attribute the passage of the 1972 legislation to this event, overlooking the myriad other contributing developments. But the committee saw that the patient was a family man, in his prime working years, who could be rehabilitated and returned to gainful employment—with help from his government. Ultimately, the ESRD entitlement was added to Medicare because the moral cost of failing to provide lifesaving care was deemed to be greater than the financial cost of doing so. ↪

Many things have changed since 1972. Responsible voices are suggesting that perhaps we should treat fewer patients with dialysis.⁴ And data are increasingly available indicating that among some elderly patients with multiple coexisting conditions, dialysis does not increase survival.⁵ These suggestions should be considered seriously, but they should be approached with great caution and humility—as the 2009 controversy over “death panels” demonstrated, such an issue can all too easily become a political football.

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Bundled Payment for ESRD — Including ESAs in Medicare’s Dialysis Package

Will this new payment approach effectively contain costs associated with treating patients with end-stage renal disease or could it compromise their care?

By John K. Iglehart

In response to a congressional mandate, Medicare has introduced a more constrained method of paying for services covered by its end-stage renal disease (ESRD) program—a method with benefits and risks for patients and providers alike. In the Medicare Improvements for Patients and Providers Act, Congress bundled into a package most of the services provided to dialysis recipients and directed Medicare’s administrators to establish a fixed compensation amount for dialysis facilities. This system, which went into effect January 1, trims payments to ESRD facilities by 2 percent overall and reduces “incentives to overuse profitable, [previously] separately billable drugs,” particularly erythropoiesis-stimulating agents (ESAs),¹ because studies showed that such overuse harms patients.² In a first for a Medicare-covered service, the law also includes a provision requiring dialysis facilities to meet certain quality standards or face a separate reduction (of up to 2 percent) in their payments.

In bundling a more complete set of ESRD services for a fixed reimbursement, Congress created an incentive for dialysis facilities: they can pocket the difference if Medicare payments are higher than the cost of delivered services but must absorb any expenses exceeding the fixed payment amounts. Some providers may take this feature as an incentive to stint on services in order to reap higher returns. To avert this possibility and more actively track patient outcomes, as Congress requires, the Centers for Medicare and Medicaid Services (CMS) pledged to have “a comprehensive monitoring strategy in place when the payment system is implemented January 1, 2011.”

Since 1972, when the Medicare ESRD program was established, Medicare has provided near-universal coverage to Americans, regardless of their age or income, who are eligible for Social

Security and have permanent kidney failure necessitating either dialysis or kidney transplantation. (If the patient is covered by an employer-sponsored health plan at the time of diagnosis, that plan must be the primary payer for the first 33 months of treatment.) Nearly all experts regard kidney transplantation as preferable to dialysis, but since a limited number of kidneys are available for transplantation, 70 percent of patients with ESRD undergo dialysis.

In 2008, Medicare made payments for outpatient dialysis services provided to about 382,000 beneficiaries by some 600 hospital-based facilities and 4,300 independent facilities. In the United States, blacks, Native Americans, and Hispanics had the highest rates of ESRD—425, 333, and 310 per million population, respectively, in 2008, according to the U.S. Renal Data Systems—which stem primarily from a high incidence of diabetes; among whites in the United States, the ESRD rate is 117.8 per million. In recent years, the number of hospital-based ESRD units has decreased, while the number of free-standing facilities has grown. Two publicly traded companies (DaVita and Fresenius Medicare Care) operate the majority of the free-standing facilities and provide dialysis services to about two thirds of all patients with ESRD. In 2008, Medicare expenditures for all ESRD-related services, including hospitalization but not Part D drugs, totaled \$26.8 billion; including spending by private health plans, the total U.S. costs for ESRD were \$39.5 billion.

Long Time Coming

Congressional action mandating fixed payment for an expanded bundle of ESRD services was a decade in coming: the Medicare Payment Advisory Commission (MedPAC) recommended it in

2001,³ having concluded that ESRD facilities had strong incentives to control the cost of services already packaged in a more limited bundle covered by a tightly constrained fee, but little or no incentive to control the costs for services directly billable to Medicare, including those for ESAs, intravenous iron, antibiotics, and vitamin D. Medicare spending for these drugs therefore “increased dramatically,” according to the CMS. The heavy use of erythropoietin by dialysis facilities began to decline in 2007, after the CMS began requiring a black-box warning on the drug label regarding the dangers of its overuse.

The final rule guiding the expanded service bundle for ESRD was published last August.¹ It set a base bundled-payment rate of \$229.63 per treatment (to be updated annually), with payments adjusted for factors including age, body size, and co-existing conditions. The rule stipulates that Medicare’s total projected ESRD payments in 2011 should be 2 percent lower than they would have been under the previous approach. The new payment rate applies only to dialysis facilities; nephrologists will continue to be compensated for outpatient care for patients with ESRD on the basis of the frequency of their visits, with a cap of \$303 for four encounters each month and lesser amounts for fewer visits. Physicians bill on a fee-for-service basis when they provide care to hospitalized patients with ESRD.

On January 5, 2011, CMS issued another rule establishing three quality measures that its administrator, Donald Berwick, predicted would focus dialysis facilities “thoroughly” on delivering high-quality care. Two of the measures apply to anemia management and hence ESA use—the proportion of patients with well-below-normal hemoglobin values (less than 10 g per deciliter) and the proportion with above-normal values (greater than 12 g per deciliter). The third measure captures patients’ urea reduction ratio. The CMS will begin using the quality measures in January 2012, and failure to achieve the set thresholds will trigger payment reductions.

The quality of care delivered by dialysis facilities has periodically come under scrutiny from MedPAC and the Government Accountability Office and has sometimes been found wanting. Recently, a series of investigative articles published by ProPublica identified many shortcomings in dialysis care, including a lack of CMS oversight.⁴ Reacting to the articles, Barry Straube, who was CMS’s chief medical officer until he retired from the agency on January 31, said: “There is definitely truth that CMS, in its regulatory role, has been unable to conduct as many surveys of dialysis facilities as are called for. We are stymied by the inadequate funds that Congress provides to perform thorough regulatory oversight for all of the 17 different provider sites that CMS is responsible for.” Sen. Charles Grassley (R-IA) has asked Berwick to explain what steps the CMS plans to pursue to improve oversight of dialysis clinics.

A Good Thing?

Reaction to Medicare’s new approach has, in general, been favorable, and particularly so in the cases of DaVita, Fresenius

Medical Care, and the analysts who track their stocks; analysts at Bernstein Research, for example, argued that “bundled pricing is likely to be very lucrative and will make Medicare patients more profitable.” Both DaVita and Fresenius provide supplies as well as dialysis services, and Fresenius also manufactures and sells equipment, so both are positioned to fare very well under the new payment approach.

The American Society of Nephrology (ASN) is less sanguine about the new approach. Joseph Bonventre, ASN president (and chief of the renal division at Brigham and Women’s Hospital, Boston), said that the “ASN is concerned about the potential for undertreatment of ESRD patients—particularly in terms of anemia management and dialysis time.” The ASN is calling for a strong system for monitoring not only these activities but also “outcomes such as hospitalizations and mortality.” Keith Johnson, chair of the board of Dialysis Clinic Inc., the largest not-for-profit dialysis provider, expressed concern about the rule’s impact on midsized and small organizations, “none of which has access to the discounts afforded the two large publicly traded companies.” And in a survey of 75 medical directors of U.S. dialysis centers, respondents predicted that “financial pressures on the smaller [ESRD] players could lead to continued industry consolidation,” a trend that could have an adverse effect on mortality among patients.⁵

The number of patients with ESRD has grown steadily and will continue to grow as the population ages and the prevalence of diabetes, hypertension, and obesity increases. Under an amendment that Congress, acting on a humane impulse, enacted hastily in 1972, Medicare has covered the cost of life-sustaining ESRD care for more than a generation at an average annual cost ranging from \$26,668 for transplant recipients to \$77,506 for patients receiving dialysis (2008 data). Faced with a new fixed-payment model, potential penalties, and looming changes under the Affordable Care Act, dialysis providers will have to manage new trade-offs that will affect patients, facilities, and their bottom lines. **MM**

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Hand Transplantation

By Hatem Amer, M.D., Brian T. Carlsen, M.D., Jennifer L. Dusso, Brooks S. Edwards, M.D., and Steven L. Moran, M.D.

■ The first successful hand transplant was performed in 1998, opening up a new possibility for patients who have suffered mutilating hand injuries. Since then, more than 60 such procedures have been performed throughout the world. This article describes the evolution of hand transplantation, outcomes of patients listed in the International Registry of Hand and Composite Tissue Transplantation, and ethical issues involved in hand transplantation. It also describes the hand transplantation program at Mayo Clinic, which was established in 2010.

Hand and upper limb injuries account for approximately 10% of all emergency department visits.¹ Such injuries are not uncommon in agricultural states such as Minnesota, and many times they can be devastating. In the case of mutilating hand injuries, surgeons often cannot replant the severed parts, requiring patients to be treated with amputation and fitted for a prosthetic limb. Because upper-limb prostheses do not provide sensation and fine motor control, they are an inadequate replacement for the lost hand or arm for many patients, particularly those with bilateral amputations. Hand transplantation is a new option for patients in which the missing part is replaced, allowing for re-establishment of sensation and fine-motor control.

Over the past decade, hand transplantation has become an established means of limb reconstruction for patients with severe injuries to the hand and forearm. Since 1998, more than 60 hand transplants have been performed successfully around the world. Mayo Clinic established the first nonexperimental hand transplantation program in the United States last year (see “Mayo Clinic’s Hand Transplantation Program”). Hand transplantation, like face transplantation, is a form of vascularized composite allotransplantation (VCA). Similar to solid-organ transplantation, VCA involves the transfer of living tissue from a donor to a recipient. In the case of a hand transplant, the transplanted hand requires a vascular connection in order to survive, and the patient requires standard immunosuppression to prevent rejection. Nerve regeneration into the transplanted tissue is required for sensation within the skin and reanimation of muscles within the transplanted tissue. VCA should be differentiated from acellular allografts such as tendon grafts and bone allografts, which have been used in orthopedic surgery for years, as those grafts are only structural in nature.

This article provides a brief overview of the current state of hand transplantation and the development of Mayo Clinic’s hand transplantation program.

History of Hand Transplantation

Hand surgeons are often called upon to reattach severed parts. Fingers, thumbs, hands, and forearms have all been successfully replanted since the initial reports of arm replantation by Malt and McKhann in 1962^{2,3} and thumb replantation by Kamatsu and Tamai in 1968.⁴ Hand transplantation was a natural extension of this technical procedure for those patients who were not candidates for reattachment.

The first attempt at hand transplantation was made in Ecuador in 1964 but failed because of problems with inadequate immunosuppression.^{5,6} During the past three decades, immunosuppressive medications substantially improved with the development of the calcineurin inhibitors cyclosporine and FK-506 (tacrolimus) as well as the potent antimetabolite mycophenolate mofetil (MMF). These medications have allowed for improvement in solid-organ transplantation and for long-term survival of limb transplants in animal models.⁷⁻⁹

The biggest obstacle to hand and face transplantation has been the perception that the skin is one of the most antigenic organs.¹⁰ The idea that skin rejection would be an insurmountable barrier to hand and face transplant was proposed by Dr. Joseph Murray, a plastic surgeon noted for performing the first kidney transplant in identical twins and who later won the Nobel prize for his work in transplantation medicine.¹⁰ Ironically, it would be Murray’s own research fellow, Dr. Jean-Michel Dubernard, who would perform the first successful hand transplant in 1998 and show that rejection could be controlled with the use of standard immunosuppression.¹¹ A worldwide voluntary registry was created in 2002 to track patient progress following VCA and report outcomes.¹²

Hand Transplant Outcomes

The International Registry of Hand and Composite Tissue Transplantation (IRHCTT) published the most extensive and comprehensive outcomes data regarding hand transplantation in 2008 and 2010.^{13,14} Follow-up was available on 33 patients

who had undergone 49 hand transplants (17 unilateral and 16 bilateral) and two digit transplants. Patients who have elected to undergo hand transplantation have tended to be younger, with an average age of 32 years (range 19 to 54 years), and male. Follow-up within the IRHCTT reports extend from one month to 11 years.^{13,14} Time from injury to transplant varied from two months to 34 years.¹³ Patient survival following hand transplantation stands at 100% within the United States.

Current long-term graft survival among patients in Europe and the United States is better than 94%. Immune-mediated rejection has been the primary cause of graft loss.^{12,14} The first case of graft loss occurred in 1998 in Lyon, France, with the first unilateral hand transplant patient; pathologic specimens of the rejected hand showed evidence of lichenoid-like lesions, which can also be seen in cases of graft versus host disease.^{12,13} Rejection occurred after the patient stopped taking his immunosuppression medications. The only case of graft loss in a U.S. patient was the result of ischemia caused by fibro-intimal hyperplasia. Fibro-intimal hyperplasia is thought to be a form of chronic rejection similar to that which has been described in heart transplant recipients.¹⁵

There has been debate over what is the best choice for immunosuppression for hand transplant patients. The majority of procedures have involved an induction process consisting of antithymocyte globulin, tacrolimus, MMF, and corticosteroids. Maintenance therapy for most patients has involved continuation of MMF, tacrolimus, and corticosteroids; this drug combination is similar to that which is currently considered standard treatment in solid-organ transplantation.^{12,16,17} Modifications of this regimen have been reported, and in the IRHCTT study, 21.7% of recipients received only steroids and tacrolimus for maintenance therapy, whereas 8.7% were switched to sirolimus; 8.7% of recipients received corticosteroids, low-dose tacrolimus, and everolimus; 4.3% received sirolimus and MMF. Thirteen percent of patients underwent withdrawal of corticosteroids at some point during the follow-up period.^{12,13} The reason for switching from tacrolimus to sirolimus or everolimus is usually the patient's inability to tolerate the medication.

There has been an effort to minimize corticosteroid dosing because of the medications' side effects. Cushing syndrome, weight gain, dermatitis, and mood swings have been observed. Metabolic complications have been seen in up to 50% of patients and have included hyperglycemia and increased creatinine values. Most of these adverse effects have been transient and reversible. One patient required bilateral hip replacements as a result of corticosteroid use; and one has developed end-stage renal disease requiring dialysis eight years after transplant.¹⁴

The majority of patients in the IRHCTT study (87%) have developed opportunistic infections, including cytomegalovirus, *Clostridium*, and herpetic infections. The incidence of metabolic complications and opportunistic infections in hand transplant patients appears to be similar to that of solid-organ transplant patients. Newer corticosteroid-tapering protocols or corticosteroid-

Mayo Clinic's Hand Transplantation Program

After extensive review of outcome studies for hand transplantation, Mayo Clinic decided to start the first non-experimental hand transplantation program in the United States. Mayo began screening patients in 2010 and is currently listing them for the procedure.

Nine hand and microsurgions on the Rochester campus are participating in the program in addition to specialists in transplantation medicine, immunology, transplant infectious disease, dermatology, pathology, radiology, and rehabilitation.

A dedicated transplant psychiatrist coordinates the patient-screening process, which includes psychological testing, involvement of the family in the decision, and a detailed analysis of the patient's support network. Hand transplant coordinators manage screening of potential recipients, coordinate the activities at the time a donor becomes available, and arrange for follow-up care. Designated hand therapists perform daily sessions once transplantation has taken place.

For more information about hand transplantation and Mayo Clinic's program, go to www.mayoclinic.org/hand-transplant or call 507/266-0446.

sparing therapies have been tried in addition to new antilymphocyte agents as well as tolerance-inducing protocols; but it is still too early to assess the benefit of these protocols over standard immunosuppression or evaluate their long-term safety.^{12,18}

Despite immunosuppression, acute rejection episodes occurred in 85% of patients within the first year; however all episodes of acute rejection were controlled with modification of immunosuppressive medications. Acute rejection, in cases of hand transplantation, is evaluated through skin biopsies. Rejection episodes are usually heralded by the development of a rash or dermatitis. Skin biopsies show evidence of lymphocytic infiltration in cases of acute rejection. Management of rejection episodes in hand transplant patients is similar to the management of rejection in solid-organ transplant patients. Hand transplant patients appear to have better survival rates than patients who have received solid organs when immunosuppressive protocols are followed properly.^{18,19} The majority of acute rejection episodes may be managed with topical or systemic corticosteroids and topical tacrolimus.¹² Deterioration in hand function has not been noted following rejection episodes.^{12,17}

Functional outcomes have been very encouraging, with all patients recovering protective sensibility, 90% recovering tactile sensibility, and 82.3% recovering discriminative sensibility.¹⁴ Muscle recovery begins with the extrinsic flexor and extensor groups, allowing some patients to perform grasp-and-pinch

activities shortly after transplantation. Recovery of intrinsic muscles can take up to 15 months. Recovery of intrinsic muscle function has been confirmed by electromyographic studies in several hands.^{16,19} Extrinsic and intrinsic muscle function has allowed patients to perform most daily activities, including eating, driving, grasping objects, riding a bicycle or motorbike, shaving, using the telephone, and writing. In addition, functional MRI has demonstrated that after transplantation, hand representation is regained within the sensory and motor cortex of the brain.^{20,21}

Brandacher and colleagues reported that the most significant clinical improvements occur during the first three years following transplant, with minor improvements occurring after that. Discriminative sensation has been identified in all forearm transplantations; this gives great hope to patients with extremely disabling injuries.¹⁷ Nerve recovery is thought to take place at a rate of 1 mm a day from the point of traumatic injury. Thus, the more proximal the transplantation, the longer it takes to recover sensation within the hand. Interestingly, it has been noted that tacrolimus, one of the immunosuppressive medications commonly used in hand transplantation, has been able to accelerate nerve recovery, potentially shortening the period of time necessary for sensory return within the hand.²²

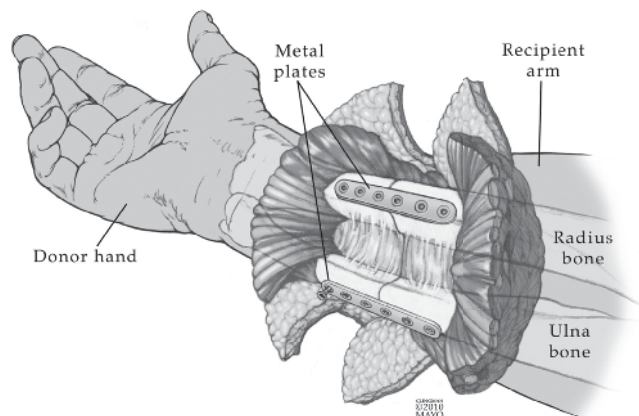
The IRHCTT study also found patient quality-of-life scores improved significantly in more than 75% of transplant recipients. Bilateral hand transplant recipients were only slightly more satisfied than unilateral hand transplant patients. In addition, the majority of patients have been able to return to work following surgery.^{13,14,17}

In summary, the IRHCTT report shows that after 11 years of clinical follow-up, hand transplantation is technically feasible and that results are encouraging as long as patients adhere to their immunosuppressive regimen and receive adequate physical therapy. Immunosuppressive protocols currently used in solid organ transplantation have proved to be sufficient to prevent rejection after hand transplantation. From a functional point of view, a remarkably good recovery of sensibility has been documented in all transplanted hands. In particular, protective sensation was achieved in all patients within 12 months. As time progressed, 90% showed tactile and 72% discriminative sensibility, thus providing a true benefit over prosthetics.^{12,13}

.....
The Transplant Procedure

Any patient in good health between the ages of 25 and 60 who has suffered unilateral or bilateral arm, forearm, or hand loss may be a transplant candidate. Exclusion criteria are the same as for solid organ transplantation: active hepatitis B or C, viral encephalitis, or active malignancy. Additional exclusion criteria include autoimmune inflammatory arthritis; extensive or severe osteoarthritis; and any neuropathy that could adversely affect the recovery of sensation and motor function within the hand such as inherited peripheral neuropathy, inflammatory (axonal or demyelinating) neuropathy, systemic disease with associated neuropathy (diabetes, alcoholism, amyloidosis), and toxic neuropathy (heavy metal

Figure 1
Attachment to the Bones



Plates and screws are used to attach the donor and recipient forearm bones during the first portion of the transplantation procedure.

Courtesy of Mayo Clinic

poisoning, drug toxicity, industrial agent exposure).

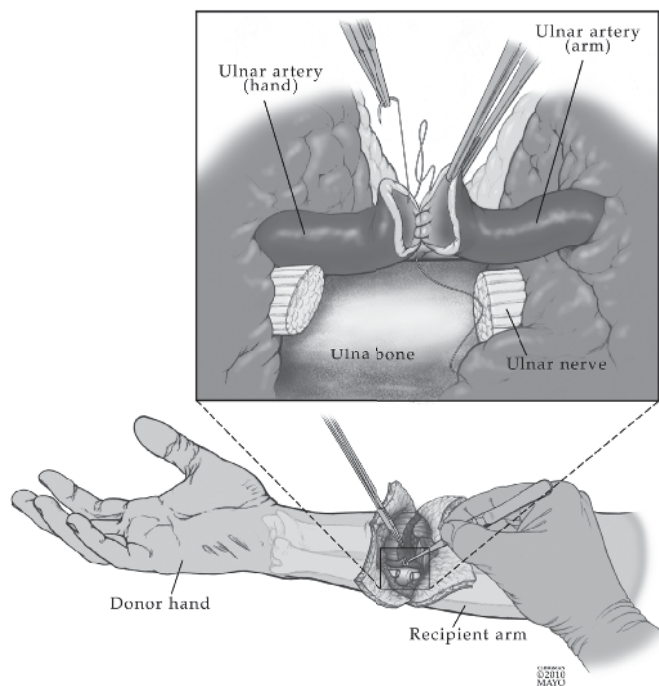
The organ donation and retrieval process is coordinated through LifeSource, the organ procurement organization for Minnesota and North and South Dakota. Donor hands are matched for sex, size, skin color, and blood type. Of the 49 limbs reported in the 2010 IRHCTT study, 28% had six HLA mismatches, 20% had five, 12% had four, and 32% had three. No zero-mismatch transplants were reported.¹⁴

Donor arms are usually removed at the level of the distal humerus. This provides additional tissue that may be used for nerve grafting or tendon grafting during surgery. In addition, it minimizes procurement time so as not to interfere with the retrieval of other solid organs.

The surgery involves preparation of the recipient's stump or injured extremity by identifying the bones, tendons, nerves, and blood vessels. The first step is attachment of the bones using standard plates and screws used in the management of forearm fractures (Figure 1). Blood flow is then re-established in the limb by anastomosis of the arteries and veins (Figure 2). Muscle and tendon repair is then carried out, followed by nerve repair. Finally, the skin is closed. Cold ischemia time has ranged from 50 minutes to 12 hours (mean: six hours, 12 minutes) and is largely dependent on the geographic distance between donor and recipient hospitals.¹³ More than five surgeons are typically involved in hand transplants, and the procedures last between 12 and 24 hours.

Following surgery, hand therapists perform daily sessions. Rigorous on-site hand therapy can continue for up to three months following surgery in cases of bilateral above-elbow transplantation. Maintenance of passive joint motion and prevention

Figure 2

Re-establishing Blood Flow

Once the bones have been secured, the arteries are anastomosed using fine suture with the aid of the operating room microscope.

Courtesy of Mayo Clinic

of contracture are essential to preserving normal motion as nerve function slowly recovers. Medical monitoring following transplantation includes doing routine skin biopsies from the transplanted hand to check for signs of rejection, as well as routine blood work to ensure appropriate levels of immunosuppressive medications.

Ethical, Psychological, and Financial Considerations

Ethical issues are a foremost consideration in hand transplantation. Hand transplantation is considered life-enhancing as opposed to life-saving; thus extreme care must be taken when explaining to the patient the risks associated with the procedure and the necessity for long-term compliance with the immunosuppressive regimen. Ensuring patients will have life-long access to appropriate immunosuppressive drugs prior to transplantation is necessary in the planning process.

It has been well-established that successful outcomes depend on a healthy doctor-patient relationship. Klapheke, who published the psychiatric results and observations associated with the lone U.S. hand transplant failure, has noted that the key indicators for success are the patient's ability to form alliances with his or her health care team, intellectual and emotional development, and body image, and whether he or she has untreated or ongoing post-traumatic stress disorder.^{23,24} During a transition period, the hand must be successfully integrated into the patient's sense of self, and ongoing psychiatric and social support are provided.^{25,26}

Hand transplant procedures performed in the United States have been supported by philanthropic grants, NIH funding, and grants through the Department of Defense. As hand and face transplant procedures become more common, portions of the procedure may be covered under some insurance plans. **MM**

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Regenerative Medicine

A Reality of Stem Cell Technology

By Andre Terzic, M.D., Ph.D., Brooks S. Edwards, M.D., Katherine C. McKee, and Timothy J. Nelson, M.D., Ph.D.

■ Regenerative medicine aims to restore homeostasis through a broad spectrum of strategies ranging from transplantation of donor organs to augmentation of innate healing processes. Its first clinical application emerged five decades ago when bone marrow-derived stem cells were used to replace defective progenitor cells. Since then, a variety of technological advances have expanded its scope. Most recently, the advent of natural or bioengineered stem cell products for tissue repair has inspired hope that the toughest obstacles in transplant medicine—the shortage of organs and organ rejection—might be overcome. This article describes the evolution of regenerative medicine and some of the ways it is being used in research and clinical practice.

Transplant medicine has laid the foundation for the emerging field of regenerative medicine, as the central aim of transplantation is replacing defective tissue with functional tissue in order to heal patients with end-stage disease.¹ Over the years, tissue and solid-organ transplantation have been used to treat patients with otherwise incurable diseases such as leukemia, cirrhosis, end-stage kidney disease, and cardiopulmonary failure.² Although transplantation has proved to be extraordinarily successful for some patients, the limited availability of appropriate organs and tissues and the problem of rejection have created a need for new strategies to meet the demands.³ Regenerative medicine offers potential solutions to these critical challenges.

Once, stem cell research and solid organ transplantation were separate endeavors. Materials science and developmental biology have bridged those fields, creating the new field of regenerative medicine. The initial application of regenerative medicine occurred five decades ago when hematologists began using bone marrow-derived stem cells as a replacement for defective progenitor cells. Advances in cell, tissue, and organ engineering have since led to new possibilities.^{4,5} Today, a variety of regenerative applications are being used and tested. In many cases, standards of care and best practices have yet to be established for cell-based regenerative therapies; however, clinical trials conducted by reputable institutions are actively enrolling patients in order to accelerate the translation of these promising applications. Regrettably, unproven therapies also are being marketed directly to patients, who may need to travel to other countries to get them.

As a result of the increased awareness on the part of patients, clinicians increasingly find themselves having to pro-

vide opinions about these therapies, some of which may be harmful or inappropriate for certain conditions. Thus, primary care providers and other specialists need to be informed about the state of regenerative medicine and emerging therapies that hold promise as well as those that are merely hype.

A Stem Cell Primer

Stem cells are the building blocks of regenerative medicine. As research on stem cells progresses, new information is becoming available daily regarding breakthrough technologies that will have an impact on our ability to translate stem cell science into clinical products and services. Regenerative medicine largely draws from four stem cell populations that function as tissue progenitors: embryonic stem cells, perinatal stem cells, adult stem cells, and bioengineered stem cells.⁶ Each cell type has unique properties.

As their name implies, embryonic stem cells are stem cells derived from embryos that are the product of in vitro fertilization. These cells are pluripotent, meaning they can differentiate into all adult tissue types. Because of their differentiation capacity, embryonic stem cells are suitable for deriving tissues that are difficult to obtain such as retinal pigment epithelial cells lost in macular degeneration and other tissues damaged by disease. However, the ethical and social considerations surrounding the use of embryonic stem cells continue to foster debate and challenge our legal system.

Perinatal stem cells are derived from umbilical cord blood. Although it is frequently discarded after birth, umbilical cord blood can be stored in private facilities or in public biobanks for later use in treating diseases such as leukemia. Perinatal stem cells are considered multipotent—that is, they can dif-

ferentiate into many but not all tissue types.

Adult stem cells are present in many tissues including bone marrow, adipose tissue, and circulating blood. Unlike embryonic stem cells, adult stem cells are considered multipotent or oligopotential because their differentiation potential is restricted. This class of stem cells is most commonly used for treating lymphoma, leukemia, or autoimmune diseases that require cytotoxic treatments followed by rescue of the hematopoietic lineages and immune system. Currently, mesenchymal cells, which are derived from adult sources such as bone marrow or adipose tissue, are favored in clinical applications because they are widely accessible and because they have multipotent differentiation capacity, favorable growth characteristics, and an encouraging safety/efficacy record in clinical transplantation.⁷

Bioengineered stem cells are a recent development. Scientists have been able to create induced pluripotent stem (iPS) cells using ordinary tissues such as the fibroblasts obtained from a dermal biopsy. With reprogramming or by applying genes typically expressed in embryonic tissues, adult fibroblasts can undergo a dramatic transformation and be reset to look and feel like embryonic stem cells. In other words, bioengineered iPS cells acquire the traits of pluripotent stem cells and the ability to differentiate into all types of tissue. These cells could be the game changer with regard to organ and tissue transplantation, as their use could offer a virtually unlimited renewable pool of tissues derived from the patient's own cells, eliminating the problems of donor shortages and rejection. They also offer a way around the ethical and political concerns associated with embryonic stem cell technology. Since the advent of iPS cell technology, bioengineered stem cells have become a source for progenitor derivation, tissue-specific differentiation, and repair in preclinical studies.^{8,9}

Clinical trials using adult stem cells to treat diverse conditions have established that this approach is safe and practical; early results of treatments for ischemic heart disease show promise.¹⁰ Therapies using umbilical cord blood stem cells, embryonic stem cells, and tissue-specific progenitors derived from adult stem cell populations are being developed for early-phase clinical studies.¹¹

Emerging Applications for Regenerative Medicine

A number of developments are enabling investigators to envision new therapies and applications. The advent of bioengineered pluripotent stem cells is particularly significant.¹² The ability to recreate pluripotent stem cells from ordinary somatic tissues such as blood or dermal fibroblasts makes it possible to create therapies that might one day eliminate the need for allogeneic transplantation. Tissues that have been created using iPS technology include dopaminergic neurons (to replace those damaged by Parkinson disease), beta cells from the pancreas (diabetes), cardiomyocytes (ischemic heart disease), retinal pigment epithelial cells (macular degeneration or Stargardt disease), red blood cells (hemophilia and sickle cell disease), and hepatocytes (chronic liver diseases). At Mayo Clinic, we have pioneered the use of bioengineered iPS cells for treating cardiovascular diseases in preclinical studies.¹³ We

Mayo Clinic's Regenerative Medicine Consult Service

Patients and their family members increasingly ask about the potential of regenerative medicine applications. To address this growing interest, Mayo Clinic has created a clinical service within its Transplant Center that provides guidance for patients and families considering stem cell-based protocols.

The Mayo Clinic Regenerative Medicine Consult Service is designed to educate patients about the risks and potential benefits of clinical trials involving stem cell therapy and to dispel myths about misleading claims about products or services sold on the open market. Physicians from the service also can connect patients with clinical trials and stem cell-based protocols, if appropriate. The service is available at the request of providers. For an appointment, contact the Regenerative Medicine Consult Service at 507/538-3270.

are now applying this technology to ischemic and nonischemic cardiomyopathy and congenital heart diseases.¹⁴ Furthermore, the ability to program human iPS cells into glucose-responsive insulin-secreting progeny has been recently refined.¹⁵

Advances in materials science are opening new avenues of research in regenerative medicine. Matrices produced from natural or synthetic sources now provide platforms for growing tissue grafts and even engineering organs.¹⁶ In fact, preclinical studies have demonstrated that it is possible to decellularize organs and leave behind only the extra-cellular matrix backbone. This natural three-dimensional scaffold provides a framework for progenitor cells to engraft and recreate the structure and function of organs such as the myocardium.¹⁶ The ultimate goal of this work is to one day build replacement organs.

Such breakthroughs are setting the stage for new clinical applications. One of the most innovative ones was a whole-organ replacement of the upper airway.¹⁷ Using a decellularized scaffold from a cadaver trachea, a team of clinicians, scientists, and engineers repopulated the matrix with mesenchymal stem cells derived from the patient's bone marrow. After months of reconstruction in the laboratory, the trachea was surgically transplanted in the patient without requiring immunosuppression.

In addition to such therapeutic applications, regenerative medicine may also lead to better methods of testing pharmaceuticals. As part of safety testing, all new pharmaceuticals must be evaluated for their toxicity. With the ability to produce human tissues using bioengineering processes, we may be able to test drugs in the laboratory before they are administered to the patient. For example, scientists are now testing cardiotoxicity of certain drugs using bioengineered cardiomyocytes.¹⁸

Regenerative medicine also may help identify patients within

Questions Patients Frequently Ask

- Are there stem cell therapies or clinical trials that can treat my condition?
- When will stem cell therapies be used to treat my condition?
- Where are they using regenerative medicine to treat my condition?
- Is a specific stem cell service safe for my condition?
- What are the differences between the various forms of stem cells?
- Are all stem cells derived from embryonic tissues?

The following websites can help you provide answers to some of these questions:

- www.clinicaltrials.gov
- www.mayoclinic.org
- <http://stemcells.nih.gov>

the transplant population who will have more aggressive disease or who may be at risk for complications following organ transplantation. In other words, we may be able to use bioengineered constructs in the lab made from tissue from the patient's own body to predict such things as the long-term effect of exposure to immunosuppression medications. This ability to identify deficiencies in the tissue-renewal process also may be useful for creating individualized therapies for a variety of other diseases as well.

Therapeutic uses are the ultimate goal of regenerative medicine. First-generation technologies are currently being studied with the aim of defining safety profiles of biologic agents while determining their efficacy in order to guide next-generation applications. This work will no doubt expand the number and type of patients who can be safely managed with tissue or organ transplantation. Autologous and allogeneic stem cells obtained from adipose tissue, bone marrow or peripheral blood, or bioengineered stem cells are already being used in applications designed to improve tissue healing in patients with ischemic heart disease,¹⁹ liver disease,²⁰ neurological disorders,²¹ endocrinopathy,²² progressive lung conditions,²³ and dermal wounds.²⁴ Mayo Clinic physicians and scientists are developing procedures and infrastructure to support and accelerate clinical trials related to human stem cell therapies.²⁵⁻²⁷

Prospects for the Future

Regenerative medicine is redefining the future for patients with end-stage organ disease.²⁸ It promises better, safer treatment at earlier stages and the possibility of cure rather than palliation of symptoms. Because its applications cross all medical disciplines, realizing the full potential of regenerative medicine will require collaboration among experts from multiple fields.

Clinical services may need to be restructured as new products and services become available, and as those products and services do more than treat specific organs or diseases. In addition, hospitals and clinics may need to dedicate resources to the field in order to efficiently navigate the regulatory processes for investigational new drug applications, FDA reporting, and monitoring the safety of their clinical activities.²⁹

In addition, they may need personnel dedicated to dealing with the growing number of patients inquiring about new treatments and services (see “Mayo Clinic’s Regenerative Medicine Consult Service”). All physicians will need to know about advances in regenerative medicine and stay well-informed of developments in bench research and clinical trials as well as the limitations of therapies. How the medical community responds may be the key to whether regenerative medicine fully realizes its potential for returning patients to health. **MM**

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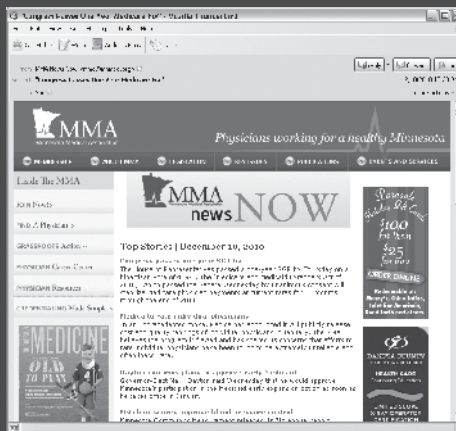
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The ACO Dilemma

Should We or Shouldn't We?

Accountable care organizations are being touted for their potential to make health care more efficient. Physicians, however, should be cautious about joining these new entities.

By Todd I. Freeman, J.D.

A shared-savings program created by the Patient Protection and Affordable Care Act (PPACA) allows accountable care organizations (ACOs) to receive incentive payments in addition to regular fee-for-service payments starting in 2012.

This provision in the PPACA comes on the heels of efforts in the private market to create similar organizations that would increase competition and, ultimately, hold down costs. Most of these efforts have been spearheaded by hospital systems, and physician providers have been aggressively recruited to join these entities.

Although the Republicans in Congress have vowed to repeal the PPACA, it is highly unlikely that the entire act will disappear. Given that shared-savings programs will be revenue generators for the federal government, they have an excellent chance of being implemented. The prevailing view is that much needs to be done to make health care more effective and cost-efficient—and that this is a first step.

What Is an ACO?

An ACO may take almost any form so long as it meets the following statutory requirements:

- The organization is willing to be accountable for the quality, cost, and overall care of the Medicare beneficiaries assigned to it;
- It will commit to the Centers for Medicare and Medicaid Services'

(CMS) shared-savings program for at least three years;

- It has a formal legal structure that allows it to receive and distribute shared-savings program payments to participating providers;
- It includes enough primary care physicians to provide care for at least 5,000 Medicare beneficiaries; and
- It promotes the tenets of patient-centered care specified by CMS, including the practice of evidence-based medicine, patient engagement, coordinated care, and the ability to report on quality and cost measures.

CMS will develop criteria to determine whether an ACO is eligible to receive shared-savings payments. The criteria will include measures of clinical outcomes, quality, and performance improvement. In March, CMS issued proposed rules that describe 65 quality measures in five categories: 1) the patient experience of care, 2) care coordination, 3) patient safety, 4) preventive health, and 5) the health of at-risk populations and the frail elderly. CMS has proposed that the quality requirement for receiving payments in 2012 may be met by complying fully with the reporting requirements related to these measures.

Should I Join an ACO?

The incentive for providers to become part of an ACO is the potential for receiving shared-savings payments. In

order to qualify, however, the Medicare beneficiaries assigned to the ACO must incur costs that fall below 98% of an “applicable benchmark” set by CMS. Therefore, when deciding whether to become part of an ACO, you will need to consider a number of issues.

Cost Versus Benefit. Because CMS has yet to finalize the regulations, the details about what will be required of an ACO are not yet known. However, it is likely that participating providers will have to comply with new reporting mandates, use standardized protocols, and have access to an electronic health record system. The concern is that ACO participants will have to make the necessary investments—in terms of dollars, staff training, and changes in operations—up front, without any assurance of a return.

Also, neither the ACO nor the physicians participating in it will be able to reliably predict whether they will receive any extra revenue from taking part in the shared-savings program. CMS is requiring ACOs that apply for the shared-savings program to opt for “one-sided” or “two-sided” participation. The one-sided approach provides less potential benefit (a maximum sharing percentage of 50%) than the two-sided approach (a 60% maximum). If the costs of an ACO’s patient population are greater than 102% of the benchmark, then the ACO must pay back a portion of this “loss.” The one-sided model imposes this risk only in the third and final year

of participation, while the two-sided option carries this risk in all three years. Are you willing to make the investments needed to be part of an ACO without any guarantee of a return?

Private Market Pressures. All providers are feeling pressure to deliver more cost-efficient care. However, the push to create ACOs could drive further consolidation in the health care market and create additional pressure, as hospitals and health systems may feel they have to merge with others in order to preserve their market share. Will your group feel it has no choice but to become part of a larger entity in order to maintain your ability to participate in health plan networks?

Political Pressures. Primary care physicians are at the heart of any ACO, as an ACO must be able to provide primary care to at least 5,000 Medicare beneficiaries in order to qualify for shared-savings payments. Primary care physicians are the ones who direct referrals to specialty physicians. Because many primary care physicians are employed by hospital systems, the hospital itself may exert pressure on specialists to join their ACO. Are you in a position to potentially alienate your referral sources by opting not to participate in an ACO?

Legal Impediments. ACOs may find themselves at risk for violating the anti-kickback rules and Stark, anti-trust, and other laws. The Federal Trade Commission, Department of Justice, Internal Revenue Service, and CMS recently invited comments on their proposals to facilitate ACOs. The proposals thus far are not friendly toward physician ownership of ACOs. What will the exceptions or safe harbors ultimately look like? What risks are you willing to take in what will likely be an uncertain regulatory environment?

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If You Decide to Join

Assuming your group decides to join an ACO, either reluctantly or enthusiastically, and is willing to share and disclose data and make the necessary investments, you need to define or resolve several other issues.

- What percentage of incentive bonuses

will go to each provider? The ACO itself needs to have a plan for how the funds it receives through the shared-savings program will be allocated to its various providers. If, for example, physicians as a category are to receive a portion of the payments, then it needs to be clear how that money will be allocated to each provider.

- Will the distribution be fair? The method for allocating money will need to distinguish between those providers who have contributed toward the efficiencies that have resulted in incentive payments and those who have not. These determinations will likely be based on utilization and outcome measurements. The ACO may simply translate the quality measures imposed by CMS for shared-savings payments into its internal method for distributing any savings to participating physicians.
- To what extent are you willing to commit? Although the rules dictate that an ACO must be committed to the shared-savings program for at least three years, it is uncertain as to the extent to which individual providers must commit. Therefore, as all of this is shaking out, it may be prudent to make relatively short-term commitments when it comes to participation (ie, only the initial three years). If, however, your practice must make a considerable up-front investment to participate, you may want to commit to a longer relationship.

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Reason for Skepticism

Both public and private payers are encouraging providers to form ACO-type organizations by offering payments on top of what they receive on a fee-for-service basis. There is a good chance that these bonus payments are fool's gold, as the criteria for receiving a portion of the savings could change from year to year. For example, if the cost threshold for providing care to a given ACO patient population in 2012 is \$10 million and the actual cost of the care provided ends up being \$8.5 million (generating a \$1.5 million

savings), it is unlikely that the threshold will remain at \$10 million after the first three years.

Rather, the new "standard" would probably be \$8.5 million, which may make it difficult, if not impossible, to generate an incentive payment. It is also possible that this approach could lead to overutilization. For example, if the new cost threshold is set at \$8.5 million and the providers in the ACO believe it is impossible for them to receive future incentive payments, they could easily revert to their old ways, causing the aggregate cost of care to go back up to \$10 million. CMS has already indicated that it will not tolerate such an increase in cost, as all ACOs will be required to share in any "losses." How these losses will be measured has yet to be determined.

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Conclusion

The idea of creating a successful ACO by the end of the year appears daunting. What is relatively certain, however, is that the current health care delivery and payment systems are unlikely to continue in their current forms. This provides a fertile environment for innovation. ACOs are but the latest experiment.

With the regulations that put meat on the bones of the requirements for ACOs still to be finalized, and with the incentives yet to be defined, there is no clear financial reason for a physician to join an ACO at this time. If the ACO concept fizzles, then new models will emerge that may provide incentives or impose requirements in order to continue participating in government or private health plans. Until that time comes, physicians may be best served by sitting on the sidelines and watching what develops. To the extent that physicians want, or feel compelled, to join an ACO, they need to pay careful attention to the requirements for participation and the up-front investment needed. **MM**

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Foggy Night

By Zubin Agarwal

It is cold
Yet the night is beautiful
Street lamps blurred by a thick fog
Car radio singing gently in the background
The road is so peaceful.

I drive further through unfamiliar territory
Destination unknown
Memories of the past fading into the darkness
Confusion dissipating into the fog
It all seems clearer now
Not sure why I stayed this long.

I drive
To where I do not know
Not once do I look back
A disappearing act worthy of a magic show

As the fog grows heavier
My eyes grow weary
Yet my vision remains
My escape route meticulously planned
The road bends to the left
And I'm gone.

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