The New World of Organ Transplantation

Penn's latest advances and future hopes for saving and improving lives through transplant technologies build on a foundation laid down by pioneering surgeons and scientists going back to the 1960s.

By Mary Ann Meyers

Two thousand miles from Philadelphia, two brothers, Telden, age three, and Stetson, two, are growing up in Billings, Montana, a city on the banks of the Yellowstone River with a view of seven mountain ranges. Both boys, the longed-for children of Chelsea and Jake Jovanovich, were conceived and born at the Hospital of the University of Pennsylvania (HUP). Their lives came about through the generosity of a woman named Cheryl Urban who felt called to donate her uterus so a childless couple could experience the joy she and her husband, Brian, have had in raising their now teenaged daughter and son.

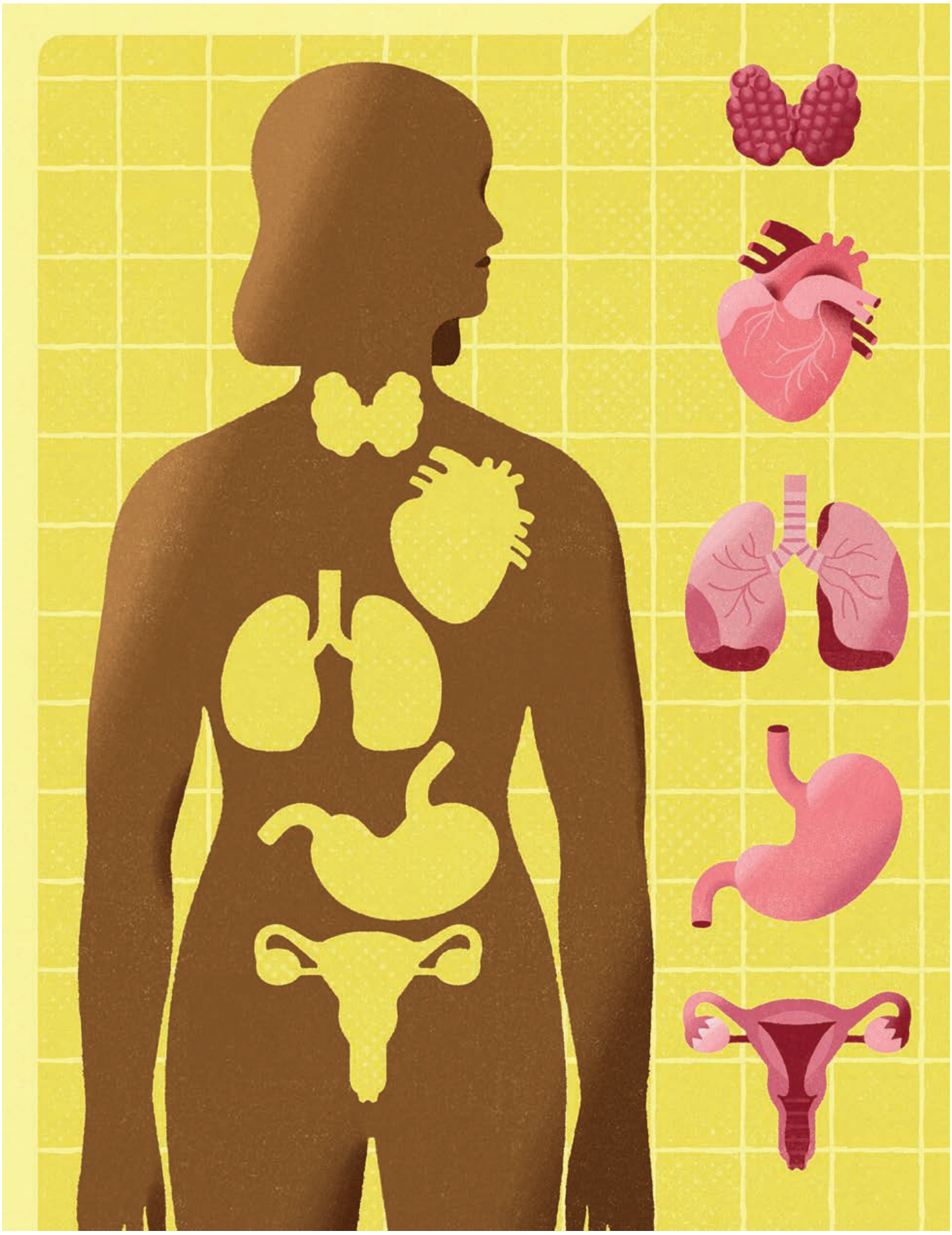
Uterus transplantation is an experimental procedure. It is sought by women who, like Chelsea Jovanovich, were born without a functional womb but have functioning ovaries, or women whose wombs have been removed because of cancer. Acceptance as a candidate involves rigorous screening and then an extensive level of medical oversight and clinical care. There have been some 100 uterus transplants performed in the world, almost half in the United States.

Kathleen E. O'Neill Gr'15, an assistant professor of obstetrics and gynecology in Penn's Perelman School of Medicine, is the coprincipal investigator of the Uterus Transplantation for Uterine Factor Infertility (UNTIL) clinical trial. She worked with the Jovanoviches throughout the long process that gave them their sons. Telden's birth in July 2021 was the first to result from a living donor uterus donation at Penn Medicine. The first baby to be born in the trial was Benjamin Gobrecht, who arrived in November 2019 and was the second baby in the nation to be born following a uterus transplantation from a deceased donor.

Six women are enrolled in the Penn program. The second woman enrolled also gave birth to two children. There were no complications in any of the five births to date in the UNTIL trials and all the children are healthy. As of the fall of 2024, the fourth and fifth recipients of donated uteruses were pregnant, and the sixth was undergoing an embryo transfer procedure. The last two women are Black, and they are the second and third uterus recipients in the world who are women of color. The University of Pennsylvania Health System funded the trial, which was designed from the start to be of limited duration and will end with the sixth recipient's last delivery. Neither government nor private insurance generally pay for fertility care nor for organ transplantation deemed experimental.

"What we are demonstrating is that the procedure is safe and reliable," Kate O'Neill says. A mother of three who earned her medical degree at the University of Michigan and came to Penn as an OB/GYN fellow in 2012, O'Neill acknowledges that uterus transplantation is not lifesaving surgery, but she makes a strong case, supported by the recipients of donated uteruses, that it is "a life enhancing" one that contributes immeasurably to human flourishing. Three other trials are ongoing at academic medical centers (Baylor, Cleveland Clinic, and the University of Alabama). Penn's audacious experiment is a testimony to its leadership in organ transplantation—one which goes back to the mid-20th century.

ILLUSTRATION BY GRACIA LAM



The University's transplantation program began in 1966 when Clyde F. Barker GM'59, then a postdoctoral fellow in medical genetics, transplanted a kidney donated by a relative into a man with end-stage renal disease at a time when the city had only one dialysis machine. It was known by then that a kidney from a living related donor provided better overall results than cadaveric donations, and advances in histocompatibility typing, including blood tests he devised himself, helped Barker find the right match. His patient lived for 48 more years with a normally functioning organ and died of coronary occlusion in his sixties. Barker, a vascular surgeon, went on to serve as chief of the transplant program he founded until 2001, as well as serving as John Rhea Barton Professor and chair of surgery for three six-year terms, the longest tenure of anyone in that leadership position in the oldest medical school and oldest university hospital in the United States.

A graduate of Cornell and its medical college, Barker came to Penn for his surgical residency in 1958. As he was finishing it, he took advantage of a month's vacation to visit some of the country's few extant transplant programs precisely because human organ transplantation was a lacuna in Penn's medical landscape. "The University was a very conservative place back then and the general view was transplantation wasn't going to work and shouldn't be undertaken," Barker says. But after scrubbing with Thomas Starzl, a pioneer in modern transplant surgery, at the Denver VA Hospital on a kidney transplantation case, he was sure that he wanted to initiate the experimental surgery at Penn.

Barker's chance to pursue his dream came after he began working as a postdoc and junior faculty member with another pioneer, Rupert Billingham, a British biologist who had been a research assistant to Nobel Prize winner Sir Peter Medawar, whose experimental demonstration of acquired immunological tolerance laid the foundation for human organ transplantation. Penn had recruited Billingham from the neighboring Wistar Institute to head the medical school's Department of Human Genetics.

A classic paper by Barker and Billingham, published in 1968 in the *Journal of Experimental Medicine*, established a fundamental law of transplantation immunology known as immunological ignorance. It means that the immune system cannot recognize the presence of a foreign body that fails to reach the host lymphoid tissue. Their collaboration helped establish Barker as one of the best-known researchers in the early years of transplantation biology, and his mentor's clout persuaded Jonathan Rhoads, Barton Professor and chair of the Department of Surgery, to let him establish a transplant program, the first in Philadelphia.

Penn nephrologists were skeptical that the new venture would succeed, as the outcome of kidney transplantation, even with a living donor, was at the time no better than 50 percent. But Barker persisted as the University's sole surgeon performing kidney transplants because he believed that the "surgical replacement of a diseased organ constituted a paradigm shift" that would "forever alter the practice of medicine while enriching multiple areas of basic and clinical science."

The patient survival rate for kidney transplants from a living donor is now nearly 100 percent after one year, and if a transplanted kidney is rejected over a longer term, a second, third, or even fourth transplant is possible. Half a century ago, however, the road ahead for Clyde Barker was marked with setbacks—as well as spectacular advances.

In 1972, he transplanted a liver from a cadaveric donor to a desperately ill recipient. While the patient survived the surgery, he died soon afterwards, and Barker called a moratorium on liver transplantation at Penn until better immunosuppressive drugs were available. In 1995, with the recruitment from UCLA of Abraham (Avi) Shaked, now the Eldridge L. Eliason Professor of Surgery and current director of the Penn Transplant Institute, and Kim Marie Olthoff, the Donald Guthrie Professor in Surgery, the program became one of the largest and most respected in the nation.

The two surgeons take particular pride in Penn Medicine's living donor program in which 60 to 70 percent of a healthy donor's liver is removed and transplanted to a recipient before "the patient is too sick," Olthoff emphasizes. The liver's ability to regenerate makes the procedure possible, but she credits the transplant infrastructure that the living donor team has built for Penn's having the best survival rates in the US—more than 90 percent five years after surgery—and very low donor complication rates for living donor liver transplants.

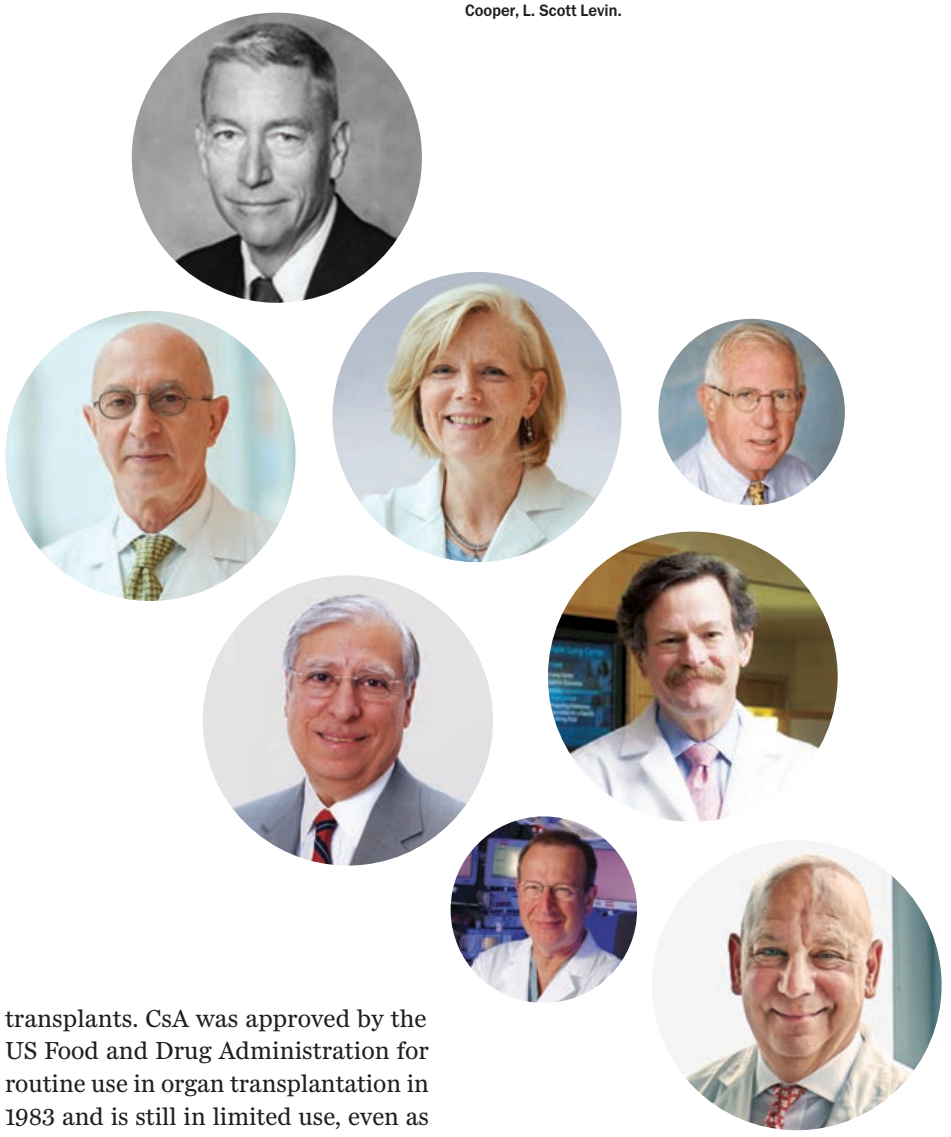
Pancreas and small bowel transplants were pioneered at Penn by Barker in the late 1980s. For many years one of his chief research collaborators was Ali Naji Gr'81, who came to HUP as a general surgery resident and vascular fellow, earned a PhD in immunology, and is now the Jonathan E. Rhoads Professor of Surgical Science II. Naji performed the first pancreatic islet transplantation at Penn in 2001 for the treatment of Type I diabetes. Using animal models, his research has helped unravel the mechanisms regulating the maintenance and loss of immune tolerance to tissue specific antigens—substances that induce the production of antibodies because they are recognized by the body as a threat—in autoimmune diseases and transplantation, a discovery that is paving the way for new approaches in immunotherapy for islet transplant patients.

The first heart transplant at HUP took place two years after L. Henry Edmunds joined the faculty in 1985 as W.M. Measey Professor and chief of cardiothoracic surgery. Edmunds, who became the Julian Johnson Professor of Cardiothoracic Surgery in 1995 and is now professor emeritus of surgery, recalls that the Commonwealth of Pennsylvania required Penn to do 12 heart transplants annually for accreditation as a heart transplantation

center. But donor organs were scarce, often depending "on a young life snuffed out in an automobile accident," Edmunds says. The last two transplants done in the first year of his program's operation took place in the nick of time just before the end of December. Today Penn does more than 50 heart transplants annually. Its cardiac transplant program is the largest in the region and among the half dozen busiest in the country with outcomes exceeding national benchmarks.

Penn Medicine surgeons also perform high-risk heart-lung and liver-lung transplants, one of the few medical centers in the US offering these exceedingly complex dual-organ procedures. Larry Keiser, who was recruited to Penn in 1991 to start a lung transplant program and would succeed Barker as Barton Professor and chair of surgery upon the latter's retirement, carried out Penn's first lung transplant. In 2005, Keiser recruited his mentor at the University of Toronto, Joel Cooper, who performed the world's first successful lung transplant in 1983 at Toronto General Hospital. Cooper, now professor emeritus of surgery, counseled younger Perelman faculty members for a decade.

From top left to right: Clyde F. Barker, Abraham Shaked, Kim Marie Olthoff, L. Henry Edmunds, Ali Naji, Larry Keiser, Joel Cooper, L. Scott Levin.



Staving off organ rejection is the proximate goal of all transplant surgeons. Attempts to thwart graft rejection have gone hand in hand with progress in the field of human organ transplantation. By 1950, when laboratory scientists had increased their understanding of tissue transplantation mechanisms, no usable method had emerged of preventing rejection in clinical practice. Barker has argued that "transplantation created the field of modern immunology rather than the other way around."

After a slow start, a fungal extract, Cyclosporine A (CsA), developed in a Swiss lab in 1976, proved transformative. The new immunosuppressive agent seemed to override major mismatches in tissue typing, and this finding cleared the way for the first use of mismatched family members and other donors for kidney transplants. CsA was approved by the US Food and Drug Administration for routine use in organ transplantation in 1983 and is still in limited use, even as pharmaceutical companies have developed a newer generation of improved immunosuppression agents. But all anti-rejection medicines can have adverse side effects, notably increased risk of infections and some cancers, skin and gastrointestinal issues, high blood pressure, high cholesterol, and diabetes, among other complications.

Upper extremity transplants, which were first reported in 1988, have been described as a technical and immunological tour de force. As vascularized composite allografts, unlike single organ transplants, they include skin, muscle, nerve, tendon, and bone. Skin is the most antigenic organ in the human body and elicits a strong immune response when recognized as foreign tissue. Preventing rejection has required high doses of immunosuppressants, and concern over the long-term effects of such therapy has been a major impediment to the growth of the only successful limb transplantation yet undertaken in the world—the transplant of cadaveric hands.

The first documented attempt at a human hand transplant occurred in Ecuador in 1964. While the procedure failed due to acute rejection requiring amputation of the transplanted hand after several weeks, a successful human hand transplant was performed in Lyon, France, in 1998, marking a significant breakthrough in the field of limb transplantation. But this technical triumph

Photos courtesy Penn Medicine, Temple University Health System

was not one the patient could handle psychologically, and the hand was removed when he stopped taking his anti-rejection medicine. In 1999, however, surgeons at the University of Louisville succeeded in what would ultimately be the first American upper extremity transplant, and that patient is currently the longest surviving hand transplant recipient in the world.

At Penn, L. Scott Levin, the Paul D. Magnuson Professor of Bone and Joint Surgery, professor of plastic surgery, and former chair of the Department of Orthopedic Surgery, assembled a large and highly experienced team that has carried out five successful hand transplants since 2011. After 27 years on the faculty of the Duke University School of Medicine, where he served as the division chief of plastic and reconstructive surgery and established Duke's human tissue laboratory, Levin was recruited to Penn in 2009 with the promise that he could establish a vascularized composite allotransplantation (VCA) program. With the support of Penn Transplant Institute director Avi Shaked, he quickly set up Penn Medicine's human tissue laboratory to serve as a teaching, research, and, not least, rehearsal facility where surgeries could be practiced on non-human models.

Noting that the "loss of a single upper limb is an emotionally and physically devastating event that results in significant impairment," Levin has written that "patients who lose both upper extremities experience profound disability that affects nearly every aspect of their lives." His first hand transplant patient, Lindsay Ess, who Levin describes as a "beautiful fashion model and designer who had just graduated from Virginia Commonwealth University," had become a quadrimembral amputee when an intestinal blockage, resulting from Crohn's Disease, caused an infection that turned her extremities into dead tissue and led to the loss of both legs below the knee and both arms below the elbow. Once engaged to be married, she had also lost her fiancé and, initially, was totally dependent on her mother for bodily care as well as assistance in all the activities essential for daily living.

But when she visited Levin at Penn after first seeing him at Duke, Ess had learned how to brush her teeth, apply makeup, drink from a cup using just her arms, and even how to text on her cellphone without fingers. She was able to walk with prosthetic legs, but living the rest of her life without hands was unfathomable. She found her prosthetic hands too heavy and of limited utility. Levin was now in a position to help her, but she had to wait for a donor, preferably a woman who had similar sized hands and skin color to the ones she once had in addition to the right blood type. The emotional burden of knowing that someone had to die for the operation to take place was hard for her to bear.

Two years after his arrival at the University, Levin was able to lead two teams of doctors and nurses, one dedicated to the right hand, the other to the left, in a bilateral transplant that took 12 hours and restored the dream of his 29-year-old patient for a mostly independent life ["Gazetteer," Jan|Feb 2012]. Her recovery, as her nerves grew into new muscle, amazed him. Now almost 14 years after her surgery, Lindsay Ess lives alone, drives a car, and competes in CrossFit competitions with wounded veterans. She remains profoundly grateful to the family of an anonymous donor even as she continues her rigorous regimen of immunosuppressive drugs, with all their attendant risks.

Given the current state of anti-rejection therapy, Levin explains, "performing an upper extremity transplant involves a different ethical calculus than solid organ transplantation, which is a lifesaving procedure. It requires weighing the benefit of improved quality of life against the cost of lifelong immunosuppression." These are difficult decisions to make, and when he joined the Penn faculty, one of the first people Levin consulted was Arthur Caplan, the founder of the University's Center for Bioethics and the Department of Medical Ethics, who was then the Sidney D. Caplan Professor of Bioethics, the first holder of a chair named for his father.

Caplan was initially skeptical when Levin described the proposed VCA program. "Risk and cost were considerations, and it has not been shown that you can replace a failed transplant. Nor did anyone know then if you could perform hand transplants on a person who hasn't stopped growing," he explains. "Furthermore, insurance companies were not willing to pay for the procedure without more data." But that data "wasn't going to be produced without further clinical experimentation," Caplan adds. For that reason, he didn't discourage Levin.

Caplan had left Penn for New York University a few months before Ess's surgery, but he has continued to follow Levin's work. The bioethicist and the surgeon agree that better outcome studies and accepted standards of clinical success must be developed, along with refining indications for transplantation, even as pharmacologists search for less toxic drugs and biologic agents to prevent rejection. Both are serving on a consensus panel at the National Academies of Sciences, Engineering, and Medicine (NASEM) to establish standards for face and arm transplantation in the United States.

Levin's other hand transplant patients include two French women referred to him by Laurent Lantieri, a friend and the director of plastic surgery at Georges Pompidou University Descartes Hospital in Paris. Laura Nataf, a quadrimembral amputee, received a double hand transplant in 2016, flying from Corsica to Philadelphia upon learning that donor hands and forearms were available. A visual artist and fashion designer, she gave birth to a daughter, now two years old, and her surgeon has a video of her changing diapers with her transplanted appendages. In 2019, Priscilla Dray's left hand and right forearm were transplant-

ed to replace body parts she lost to sepsis. Last summer Levin attended her son's bar mitzvah in Bordeaux, where he watched mother and son dance together, hands touching, in a joyous rite of passage. His most recent bilateral transplant was successfully carried out last fall when he replaced the hands and forearms of a young man from Switzerland.

No story of limb transplantation at Penn is complete or, indeed, comparable to that of Zion Harvey's ["The Gift," Nov|Dec 2015]. Zion, who had both hands and his legs below the knee amputated at age two because of staphylococcal sepsis resulting from flu, was the first child in the world to undergo a bilateral hand transplant. In 2015, at the Children's Hospital of Philadelphia, Levin's team worked with a CHOP team codirected by Benjamin Chang, then an associate professor of clinical surgery at Perelman, along with the chief of staff at Shriner's Hospital for Children Philadelphia, 40 people in all, to attach donated hands and forearms to the then eight-year-old boy from Baltimore. The ethical issues posed by the decision to proceed with the surgery were mitigated by the fact that Zion was already taking immunosuppressive drugs because the infection that robbed him of his limbs also caused his kidneys to fail, and he had received a kidney transplant from his mother.

Intensive physical therapy and occupational therapy, as Zion's brain relearned how to communicate with his hands and his muscles and tendons gained strength and flexibility, were an essential part of the healing process after his transplant surgery. He faced and overcame hurdles, with the help of his doctors, when his body tried to reject his new hands eight times, and the Penn and CHOP teams adjusted his medications to reverse the episodes. His therapists tapped into his keen interest in sports. He progressed from tossing basketballs to baseballs, culminating in throwing out the first pitch at an Orioles home game 13 months following his life-changing operation.

The exuberant personality of the child has not deserted him in adolescence. Proud that he could dress himself without help and heat up a pizza at 10; at 18, he attends high school, holds a part-time job, drives, climbs rock walls, and plays the cello. Levin and his colleagues, and their successors, will follow Zion as long as he lives, attending to his physical condition and providing psychosocial support, with particular attention to how he continues to cope with the demands of therapy and treatments. The Penn surgeon hopes that "hand transplants will become the standard of care," a cause he has been championing at the NASEM and a designation that will make the procedures more easily insurable.

Gratefulness to donors is a thread that runs through the responses of organ recipients to questions about their experience. Since 1986, the United Network for Organ Sharing (UNOS) has managed the Organ Procurement and Transplantation Network. Created by Congress, it is the place that medical centers turn to for donors. The Gift of Life Program coordinates the operating phase of donations in the eastern half of Pennsylvania, southern New Jersey, and Delaware. Predating UNOS, it was founded in 1974 by Clyde Barker and other area transplant surgeons and is the largest organ procurement organization in the United States.

Because UNTIL was a research study to determine the efficacy and safety of transplantation as a treatment for women with a previously irreversible form of female infertility, Cheryl Urban's path to donating her uterus to Chelsea Jovanovich did not go through UNOS but began when she contacted Penn directly in April 2019 after seeing a television newscast about the program, which was seeking donations from both living and deceased donors, as she was leaving for work. On the way there, she called her husband and related the story. That evening they discussed her strong inclination to donate the uterus that had carried their two children, and the next day she filled out an application online. "I was propelled toward my decision by the sense that I was being presented with an additional purpose for the wonderful life I was living as a wife and mother," she says.

The two women's procedures took place three weeks before the world shut down in the face of the COVID-19 pandemic.

Cheryl, who had studied nursing before switching to a business major in college, was invited for an interview with Kate O'Neill. They discussed the nature of the hysterectomy a woman donating her uterus would need to undergo and the risks. After a battery of tests, she was accepted as a donor.

Just before Christmas 2019, Cheryl got a call saying she was a match for a potential uterine transplant recipient. Looking ahead at her children's winter sports schedules, the Bucks County, Pennsylvania, mother said she could undergo the procedure on February 21, 2020, two months before the date originally proposed by O'Neill. Chelsea had previously undergone an *in vitro* fertilization (IVF) procedure at Penn, during which her eggs were harvested and fertilized to create embryos that were then cryopreserved for transfer into her new uterus following transplantation. She and her husband had been living in Philadelphia since November 2019 waiting for a donor. The two women's procedures took place three weeks before the world shut down in the face of the COVID-19 pandemic. Their operations were performed in two different wings of HUP. Nawar Latif Gr'18, an OB/GYN assistant professor and O'Neill's coprincipal investigator in the UNTIL trial, described Cheryl as "the most altruistic person I have ever met." Chelsea had given her doctors permission to tell her then-anonymous donor the one thing she wanted to know: Did the transplant

work? The answer was yes. Cheryl describes her reaction as "pure elation."

But it would be several weeks before doctors could be sure the transplanted organ would not be rejected, and Chelsea would have to heal from her surgery before one of her three embryos could be transferred to her new womb. The first transfer failed, but on the second try, she became pregnant. A month later, she reached out to Cheryl through her social worker. The joyfully received contact led to an exchange of emails, then telephone calls and meetings on Zoom. Just before Chelsea's delivery of her first son, Telden, by C-section on May 18, 2021, the two women met at Penn Commons. They hugged, and cried, and sat on a bench and talked for three hours.

Chelsea and Jake Jovanovich stayed close to Penn throughout the 20 months it took to create their family. They first stayed in the Clyde F. Barker Penn Transplant House, a small guest house a few blocks from HUP. A rented house in Ocean City, New Jersey, was their next home away from the home they had built in Montana in 2019, and eventually they bought a house in Lumberton, New Jersey, before Chelsea's third and last embryo was implanted, resulting in Stetson's birth on October 20, 2022. His mother had been on immunosuppressive drugs since receiving her donor uterus, and with its removal at the time of her second delivery, she was able to stop taking them. The Urbans had become family. Cheryl flew to Montana to celebrate Stetson's first birthday and shared in his second via video chat.

O'Neill is, and will always be, the boys' "Aunt Kate." Their photographs are on her phone along with those of her own children and her other four transplant babies. "Women with uterine factor infertility, an estimated 200,000 of reproductive age in the United States, have limited pathways to parenthood," she says. "There is adoption and surrogacy. My goal was to provide them an additional option—the only option that allows them the opportunity to carry and deliver their own babies."

Organs from animals, or xenografts, represent the "next new frontier" in organ transplantation's future, Markmann says.

All organ transplantation runs up against two vexing problems: the need for toxic immunosuppressive agents, if even for a relatively brief time with uterus transplants, and of chronic donor shortage. But that the procedure is entering an auspicious stage of growth is the firm conviction of Penn Medicine's Vice President for Transplantation Services, James Markmann M'87 Gr'89 GM'96, who was recruited for the newly created position in 2023 from Harvard—where he served as chief of the division of transplant surgery and director of clinical operations at the Transplant Center at Massachusetts General Hospital. Markmann, the William Maul Measey Professor in Surgical Research, has an active clinical practice in liver, kidney, and kidney-pancreas transplantation, and his laboratory works on transplantation immunology.

Markmann sees three very tangible rays of hope for meeting the challenges of toxicity and shortage. As to the former, he is optimistic that his research on strategies to improve graft survival, on immunoregulatory T cells as a means to induce tolerance to an allograft, and just-begun clinical trials of human stem cell derived islet transplantation, along with planned studies involving the simultaneous transplantation of donor bone marrow, could lead to a future for organ transplantation less dependent on immunosuppressive drugs.

To improve the availability of organs, Markmann looks to two possible sources, one of which became part of clinical practice in advanced transplant centers like Penn in 2022. "Organs taken from cadavers slowly die without oxygen," he explains. "Historically the organs were put on ice, which only sustained them for a limited period of time as, left too long, cold storage caused graft dysfunction and chronic complications for recipients. Human trials, begun in 2016, have led to the availability of *ex vivo* organ prefusion devices for each transplanted organ."

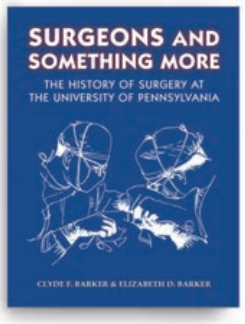
Such devices, "currently in various stages of clinical trials, mean donated organs receive oxygen and nutrients until they can be given to the recipient, thereby increasing availability of suitable organs and impacting the success of transplant procedures," Markmann says. "In liver transplants, for example, approaches with a lack of oxygenation led to a 30 percent organ failure rate. With these pumps, the quality of an organ can be assessed before transplantation, a practice that has already led to thousands of saved lives."

Organs from animals, or xenografts, represent the "next new frontier" in organ transplantation's future, Markmann adds. "CRISPR made all the difference," he says, referring to the transformative biological innovation for gene editing. It allowed scientists to knock out a retrovirus in pigs that can infect human cells in culture along with pig antigens to which humans have antibodies that could trigger an acute rejection response.

And Markmann drove to Boston last March to witness the first transfer of a genetically altered pig kidney into a male patient at Massachusetts General Hospital (MGH). "A biotech company had inactivated three genes from the pig kidney involved in potential rejection of the organ," he recalls, "and seven human genes were inserted to enhance human compatibility."

Two transplants of pig hearts into terminally ill men had previously taken place at the University of Maryland, and in April of 2024, a woman received the genetically modified kidney of a pig at New York University. The MGH patient, who was discharged from the hospital

Deep Cut



Surgeons and Something More: The History of Surgery at the University of Pennsylvania
By Clyde F. Barker GM'59 and Elizabeth D. Barker
American Philosophical Society Press, 2024, $75

"Knock it off, fellows" was, in effect, the satirical plea of a Philadelphia newspaper in 1780 to the feuding founders of the nation's first medical school. The public quarreling of William Shippen Jr. and John Morgan over personal and professional matters would "poison the air" of Penn's School of Medicine from its start in 1765 until their deaths, Clyde Barker GM'59 and his daughter, Elizabeth Barker, tell us in *Surgeons and Something More*, their masterful tale of the evolution at Penn of the art and science of healing the sick by invading, with all the attendant risks, their bodies.

Hard to hold in your hands at nearly 600 pages but very readable, the hefty, handsomely illustrated book, at once detailed and entertaining, about the techniques, tools, and, most importantly, people that shaped a branch of medicine in which the University can justly claim eminence has as its lead author the surgeon who played a key role in this history [see accompanying story]. The "something more" here is the broader context in which the development of the department of surgery is set and the fascinating biographical material highlighting the foibles as well as the feats of the 19 departmental chairs (all men so far).

Timelines help readers grasp the sweep of the story that moves from the disastrous bloodletting used by Benjamin Rush to treat yellow fever patients through the invention of absorbable sutures made from kid gloves or catgut by Philip Syng Physick—whose lecture notes were collected to produce the first comprehensive surgery text (1813) written in America—to the reign of D. Hayes Agnew M1838, beloved by his students who, upon his retirement in 1889, commissioned an unemployed artist (Thomas Eakins) to paint his portrait, now viewed as representing the transition to modern medicine through the acceptance of antisepsis.

During the short chairmanship of the crusty John Deaver M1878, we learn that surgeons returning from service in World War I were assigned to specific portions of the body, a concept ahead of its time, though motivated by Deaver's interest in maintaining his monopoly on abdominal surgery. His chief resident was I.S. Ravdin M1918, who, in pursuing basic research abroad, learned the value of collaboration with basic scientists and returned to the Hospital of the University of Pennsylvania (HUP) to focus on laboratory investigation, pioneered the practice of blood transfusions to alleviate shock from intra- and postoperative bleeding, and in 1942 organized the US Army's famed 20th General Hospital in India staffed by HUP personnel.

The brilliant and colorful Ravdin headed the department for 15 years after World War II—and ran his fiefdom, the Barkers say, like "a commanding general." His handpicked successor was Jonathan Rhoads GrM'40 Hon'60, and the authors recount his role in the development of intravenous nutrition, which was rapidly accepted and employed around the world, and, as a "stateman of science and medicine," in securing federal support for cancer research.

What the Barkers call the "turbulence" caused by the University's move to consolidate and integrate the clinical practices came to an end for surgery, a guest contributor declares, under Clyde Barker's chairmanship, a tenure marked by the dissolution of the bogus boundary between basic and clinical science.

But the story doesn't end there. In their concluding chapters, the authors highlight the work of younger surgeons—men and, at last, women, who are charting the future of Penn Medicine in its 260th year. —*MAM*

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two weeks after his surgery, died two months after the historic procedure. There was no indication that his new kidney contributed to the patient's death, but Markmann is waiting to see a full report on the case. The second porcine kidney transplant had to be removed from the recipient because it interfered with her blood flow; she died two months later. There was some evidence that the 2022 and 2023 heart xenografts were in the process of being rejected when the patients died only weeks after their surgeries. But Markmann believes that xenografts may yet provide an answer to the organ supply problem, noting that fully half of the more than 100,000 people on organ transplant lists die waiting.

Avi Shaked leads a team of researchers that in December 2023 completed an experiment to circulate a recently deceased donor's blood through a genetically engineered pig liver outside the body—a milestone in the quest for a more effective "bridge" option to support critically ill patients until a human liver transplant is available for them. Could it work for other body parts? The needs of transplant surgeons and their patients are driving innovation.

Shaked believes that "organ transplantation will continue to revolutionize medicine." The risk-reward calculus in the surgery must always be a crucial consideration. As Art Caplan has pointed out, "new forms of transplants require doctors, patients, regulators, and the public to rethink the tradeoffs between saving life, extending life, and risking the loss of life to achieve improvements in the quality of life." Some 20 years ago, in an address as president of the American Society of Transplant Surgeons in 2003–04, Shaked told his colleagues: "For our revolution to succeed we must have a clear vision of the new world we are building."

Mary Ann Meyers Gr'76, former secretary of the University of Pennsylvania, president of the Annenberg Foundation, and senior fellow at the John Templeton Foundation, is the author of *Art, Education, and African American Culture: Albert Barnes and the Science of Philanthropy* (2004 and 2006) among other works.