The 2012 Lasker–DeBakey Clinical Medical Research Award honors two scientists who developed liver transplantation, an intervention that has restored normal life to thousands of patients with end-stage liver disease. Through their systematic and relentless efforts, Roy Y. Calne (Emeritus, University of Cambridge) and Thomas E. Starzl (University of Pittsburgh) created a medical procedure that most physicians deemed an impossible dream. Some of Starzl’s and Calne’s early patients—originally diagnosed with untreatable and lethal diseases—are still thriving today, decades after their surgeries.

The liver performs many services that are vital for life. It detoxifies harmful substances, manufactures essential materials for the body, stores energy, and secretes bile, which helps digest fats. In the late 1950s, serious liver diseases were fatal, and treatment prospects looked bleak. The idea of transplanting any organ from an unrelated individual seemed foolish to most experts. Rejection—the process in which a body’s immune system attacks unfamiliar tissue—posed a seemingly insurmountable obstacle, and other aspects of liver biology presented overwhelming challenges. This organ supplies clotting factors, and liver disease produces tremendous pressure in the veins, creating a sea of wormlike vessels many times bigger than usual in which a tiny nick can trigger massive blood loss. Patients with liver disease, therefore, bleed extremely easily and often uncontrollably. Furthermore, multiple vessels deliver blood to the liver and drain other substances, so surgical manipulation of the organ is anatomically complicated.

Learning new tricks from dogs

In the late 1950s, a particular feature of liver anatomy captured Starzl’s attention. Two large blood vessels serve this organ, one of which—the portal vein—runs through the gastrointestinal tract and pancreas, picking up substances from those sites. Controversy boiled about whether the nutrient- and hormone-rich portal blood contributes to liver health. To study this question, Starzl developed several liver-transplant procedures and gradually refined them. In 1958, his canine patients began surviving the operation. Although Starzl had not intended the surgery as a step toward human liver transplantation, the work established that the technique was feasible, and he set his sights on bringing it to the clinic.

By 1960, Starzl (then at Northwestern University, Chicago) and the late Francis Moore (Peter Bent Brigham Hospital, Boston) had independently tackled many problems associated with the dog liver replacements. Cutting off the blood supply damages the liver, for instance, so Starzl devised preservation methods: He cooled the donor organ by infusing it with chilled solutions, a practice that is now universal. Both groups also worked out key technical aspects of the operation. For example, when they realized that dogs died from acute heart failure when they clamped two particular veins, they each devised blood-bypass methods that permitted surgical success.
Enter immunosuppression

Despite this progress, skepticism flourished about the utility of any type of organ transplantation. Perfecting an operation from which few would benefit—due to the apparently impenetrable immune barrier between non-identical twins—seemed futile. Nevertheless, a handful of scientists pursued the venture in animals, and between 1959 and 1962, surgeons performed seven initially successful human kidney transplantations. Before their operations, the patients underwent total body irradiation to thwart immune attack.

Interested in the immunological aspects of transplantation, Calne had been studying irradiation in dogs. Because the procedure was extremely toxic, he began testing chemicals that might thwart rejection. In 1960, Calne (Royal Free Hospital, London) and, independently, the late Charles Zukoski (Medical College of Virginia, Richmond) deployed a drug, 6-mercaptopurine, that was known to block immune responses to foreign proteins. This agent kept some dog kidney recipients alive for months and demonstrated for the first time that chemical immunosuppressants could fend off rejection. Calne then used 6-mercaptopurine in a few patients and achieved some benefit. Soon afterward, he obtained better results—in dogs—with azathioprine (Imuran), a chemical relative of 6-mercaptopurine. His success inspired Joseph Murray at the Brigham to try it in humans. In 1962, Murray used azathioprine in a kidney transplant patient, who survived for 17 months.

However, when most azathioprine-treated transplant patients did not surpass six months' survival, enthusiasm plunged in the nascent organ-transplant community. Working with dogs, Starzl made crucial improvements: He began azathioprine before the operation and added the steroid prednisone.

Starzl opened a kidney transplantation program in Denver (University of Colorado), informed by his animal work, and started obtaining excellent outcomes: One of his patients is alive today, 49.5 years after the surgery. He also overturned conventional wisdom about rejection, which held that the process was unstoppable once it started. Starzl decided to proceed with a liver-transplant program, using the dual immunosuppressive regimen he had developed for the kidney.

Launching livers

In March, 1963, Starzl attempted the first human liver transplant, on a child with biliary atresia, a condition in which the bile-carrying tubes are blocked. The patient bled to death during the operation. Although the next several liver recipients died within a few weeks after their surgeries, some of them endured long enough to demonstrate that transplanted livers could function.

Surgeons worldwide declared a moratorium on the procedure and analyzed what had gone wrong. The transplanted livers, retrieved at autopsy, showed no signs of rejection—a significant achievement. Instead, bacterial infections, caused in part by the bypass tubing that had been essential for dogs, had killed most of the patients.

During the next few years, Starzl improved the procedure in many ways. He used an antibody, antilymphocyte globulin (ALG) that restrains rejection and demonstrated that portal-vein blood contains substances that keep livers healthy. Until then, experts in experimental liver transplantation had been weighing the merits of adding a second liver rather than replacing the
diseased organ. Because supplemental livers were not hooked up to the portal vein, the finding clinched the decision to opt for replacement.

During this period, Calne read that a few unmedicated pig liver recipients survived for a surprisingly long time. This result intrigued him and drew him toward the liver. He subsequently showed that liver grafts in pigs are tolerated better than other transplant tissue, an observation that presaged future findings in humans.

Starzl reopened the Denver liver program in 1967 and adjusted patient care based on the innovations he had developed. He treated patients with three drugs—azathioprine, steroids, and ALG—and survival times began to exceed one year. The world’s longest survivor has now carried her transplanted liver for more than four decades. Although most in the medical community still considered the procedure too risky, Calne forged ahead to open the second liver transplantation program in 1968.

Full steam ahead

Key advances in immunosuppressive drug regimens further improved organ-transplant outcomes. Calne pioneered the use of the most potent agent yet—cyclosporin A—which he brought to the clinic in the late 1970s. The compound could harm the kidneys, but Starzl ushered it to its full potential by demonstrating that the toxicity could be reduced by combining it with prednisone. Finally, most liver transplant patients were surviving for longer than a year.

In 1983, the U.S. Surgeon General convened a Consensus Development Conference for liver transplantation, which concluded that liver transplantation had progressed past “experimental procedure” status into a “clinical service.” The treatment had finally gained acceptance and centers worldwide rushed to offer it.

Clinicians continued to seek alternative agents that combat rejection while minimizing adverse side effects. In 1989, Starzl (by then in Pittsburgh) introduced FK506 (Tacrolimus), a compound that differed chemically from existing immunosuppressants, first in individuals who were rejecting organs despite conventional regimens and then in new transplant patients. FK506 gained fast-track U.S. Food and Drug Administration approval in November 1993. Calne next added rapamycin to the armamentarium—a chemical that resembles FK506 structurally, but has a different mechanism of action and toxicity profile. He also pioneered the use of the powerful monoclonal antibody immunosuppressant, alemtuzumab (Campath), first to treat rejection and then as a pre-emptive therapy to prevent that complication altogether.

Human liver transplantations have not only saved lives, but have provided insights into medical conundrums. In 1969, a liver transplant by Starzl alleviated symptoms of Wilson’s disease, a condition that causes copper accumulation in many tissues, and thus revealed that the illness’s roots lie in the liver. Fifteen years later, Starzl transplanted a liver into a girl with two defective genes for the low-density-lipoprotein (LDL) receptor. Her improved blood LDL profile showed dramatically that this organ houses the receptors that remove cholesterol-carrying LDL from the blood.

Today, liver transplantation has taken hold in sophisticated medical practice across the world, and some patients even survive long-term without medication. In the United States, surgeons use the procedure most commonly to benefit adults who have sustained liver scarring—or cirrhosis—from hepatitis C infection and children who have biliary atresia. More than half of the liver-transplant patients who underwent surgery in 1998 were alive ten years later, and in 2009, almost 50,000 Americans carried a transplanted liver.
Calne and Starzl persevered on a bold course against a backdrop of doubt. By following glints of hope, they have brought new life to thousands of individuals.

*By Evelyn Strauss*