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The evolution of transplantation is one of medicine's greatest stories. Much of it was written by Tom Starzl, who died at the age of 90 on March 4, 2017. He added a new dimension to the field of medicine by innovating and perfecting methods of replacing failing vital organs.

While there have been other contributors, there are few instances in which a single individual has been so predominantly responsible for establishing an important field. Even this underestimates Tom's influence, considering the overall impact and downstream effects of transplantation on other disciplines. For example, most would agree that modern immunology owes its maturation to transplantation rather than the other way around.

While growing up in Le Mars, a small town in Iowa, Tom enjoyed the usual boyhood activities—Boy Scouts, high school basketball and football, and playing the trumpet in a jazz band. Another experience was an uncommon one: working as a reporter for the town's newspaper, which was owned and published by his father. This may have given him a start toward becoming a gifted writer who would one day become the most highly cited medical author of his time.

After a year and a half in the Navy and then graduating from Westminster College, he was influenced by his mother, a nurse, to pursue a career in medicine. Entering medical school at Northwestern University, he supported himself as a copywriter for the *Chicago Tribune*. He then developed a serious interest in neuroscience and dropped out of medical school for a year of full-time research. He implanted electrodes deep within the brains of experimental animals. Recordings from these electrodes helped to define the ascending reticular activating system. The five resultant papers that formed the basis of his Ph.D. thesis are still being cited.

Although urged by his mentor, Horace Magoun, to remain in neuroscience, Tom instead completed medical school and then began a surgical residency at Johns Hopkins University. There he did research on cardiac physiology. In dogs, he developed a model of complete heart block and its treatment with one of the first experimental pacemakers.

After four years at Hopkins he moved to the University of Miami to complete his surgical training. There, in a laboratory that he built for himself in an abandoned garage, he continued to do research. He had become fascinated with the liver and its double blood supply, which consists of an artery and a portal vein that delivers to the liver venous blood coming from the intestine and the pancreas. He developed in dogs a model of liver transplantation, hooking up the new liver in various ways with or without a portal vein. He found that, unless portal blood was supplied, the transplant shrank and was damaged.

These experiments were performed without any thought of using transplantation to replace failing livers but only to study the physiology and metabolism of the organ. At this time, it would have been pointless to pursue liver transplantation as a therapy since there was no way to prevent rejection. Immunosuppressive drugs had yet to be discovered. So far the only human transplant that had been successful was one from an identical twin.

After he finished his residency, Tom wasn't sure what to do next. He had explored neuroscience, cardiac physiology, and liver metabolism without committing himself to a career in any of these fields. Discouraged and frustrated, he considered going into private practice to support his growing family. He remembered himself as bursting with energy and ambition to achieve something meaningful. But what? He likened himself to a missile searching for a trajectory. Ultimately, he decided to further extend his education by training in thoracic surgery. He acknowledged the criticism from his wife's family that he had become a perpetual student.

But then, just at this time, he learned that investigators in Richmond, Virginia and in London had discovered in animal experiments that the anticancer drug 6-mercaptopurine and its derivative Imuran would delay rejection of kidney transplants. He later recalled saying to himself, "Wow, this [liver transplant] operation that I developed only for study of liver physiology could be used to treat people dying from liver failure." He had found his trajectory. It would be transplantation, and he hoped especially transplantation of the liver.

Tom spent the next three years back in Chicago at Northwestern. After completing his training in thoracic surgery he returned to studies of the liver, but now with the goal of transplanting it as a treatment. Since he did not yet have access to the new immunosuppressive drugs, these studies were of unmodified transplant rejection. Rejection of his transplants always began within a few days but, occasionally and quite mysteriously without any treatment, it seemed to slow or almost stop for a time. This was provocative. Tom began to wonder if he could find a way to reverse rejection. This notion would become the key to a major breakthrough, perhaps his most important one.

In 1962 Tom accepted a faculty appointment at the University of Colorado. Also at this time he was able to obtain a supply of the new immunosuppressive drug, Imuran. He began to test it in dogs with liver and kidney transplants. He soon made a crucial observation that was missed by other investigators who were testing the same drug. They had administered Imuran as a single agent or simultaneously with prednisone or other cytotoxic drugs. Rejection was modestly delayed but it always resumed and was always fatal. For the next two years

Tom experimented with many different ways of using the drug. Eventually he found one way that allowed consistent success. When Imuran alone was given to a dog, rejection always began within days or weeks. But if he treated the dog with massive doses of the adrenal cortical drug prednisone he could always reverse rejection, something that had never before been considered possible. Subsequently, he could reduce or sometimes even stop immunosuppression without recurrence of rejection.

Encouraged by his dog experiments, Tom began to try his immunosuppressive trick in human transplants. He started with the kidney, realizing that until he could succeed with this simpler procedure it would be unwise to undertake liver transplantation. He learned that in Boston, Joseph Murray was also using the new drugs in human kidney transplant patients.

In September 1963 Tom was given the chance to reveal his exciting findings. A small conference had been organized by the National Research Council (NRC) to assess the experience with human kidney transplantation. About 25 of the world's transplant authorities were assembled. Tom, a young and virtually unknown newcomer to the field, had been invited to the meeting as an afterthought. One by one the established experts reviewed the status of the field up to this time—altogether about 200 transplants. Their results were all terrible. Less than 10 percent of their recipients had survived as long as three months. Most of their patients had been treated with total body irradiation as an immunosuppressive maneuver, and hope was expressed that the new immunosuppressive drugs might be more effective. Murray reported on his first 10 patients treated with Imuran. One had survived for a year although at the time of the conference was undergoing rejection. The other nine had died within six months. Thus the new drugs seemed no more effective than radiation. The mood at the conference was so gloomy that some participants questioned whether continued activity in human transplantation could be justified.

The gloom was then dispelled by a single presentation, the one given by Tom who described his first 30 drug-treated patients. His unique protocol had reversed rejection and allowed 80 percent one-year graft survival. Tom realized he had more surviving transplant patients by far than the rest of the world's experts combined. The audience was incredulous. The subsequent discussions were acrimonious, but eventually Tom's results had to be believed because he had brought charts detailing daily progress of each patient, including laboratory tests, urine output, and immunosuppressive drug doses.

Tom's report caused a sensation. It completely changed the outlook for transplantation. Boston surgeon and transplant historian Nick

Tilney described it as "letting the genie out of the bottle." The news of the breakthrough spread quickly. Before the NRC conference there had been only three active renal transplant centers in North America—in Boston, Denver and Richmond. As the effectiveness of Tom's innovative immunosuppression became known, within a year 50 new transplant programs began in the United States. All of them adopted the Starzl immunosuppression cocktail. In fact, Tom's protocol remained the virtual world standard for the next two decades.

Tom now felt ready to approach his primary goal, liver transplantation. But despite his extensive experience with the procedure in dogs it proved to be very difficult in humans. In 1963 his first patient, and the world's first, bled to death on the operating table. The next four died within a few days causing Tom to impose a moratorium on his program. The procedure was so violently controversial that Tom's medical colleagues refused to send him their end stage liver failure patients. For the next three years with further research and animal experiments he addressed the problems of earlier failures. One important modification was the introduction of another new immunosuppressive agent, anti-lymphocyte globulin, which Tom was the first to employ clinically. In 1967, Tom performed the world's first successful liver transplant and soon after four more that were initially successful.

For the next 10 years Tom struggled to improve his results without much success. Many of his liver recipients survived but at least half died within a year. He had proven that liver transplantation was feasible, and it was still a qualified success. However, to be accepted as a practical clinical service further improvement would be necessary.

In 1979 Tom sensed that there might be a chance for this improvement. A new immunosuppressive drug had been introduced in England by Roy Calne. After encouraging experiments in animals, Calne began to use it in human kidney transplant recipients. He found this drug, called cyclosporine, more potent than Imuran but also very toxic, leading to infections, lymphomas, and kidney failure. Other trials of the drug in Canada and Boston were similarly disappointing, causing many to believe it should be abandoned. In fact, the manufacturer seriously considered taking it off the market. But at this point Tom came to the rescue of the new drug. Once again, as he had 20 years before with Imuran by using it in appropriate doses and adding prednisone, Tom made cyclosporine work safely and so effectively that it revolutionized the field.

Shortly thereafter, in 1981, Tom moved to the University of Pittsburgh, taking cyclosporine with him. There for the next decade he worked at a furious pace, performing as many as 600 transplants a year with excellent results. His consistently successful use of

cyclosporine had transformed liver transplantation into a practical clinical service.

Tom's remarkably consistent success with cyclosporine led to its acceptance as the standard baseline immunosuppressant worldwide. It remained so until 1989 when it was proven again by Tom that rejection of liver and other organ allografts that were resistant to treatment by cyclosporine could often be reversed by an even more potent new drug that he introduced. This drug, FK506 or tacrolimus, has now in large part replaced cyclosporine as the usual baseline agent. In addition, it has allowed successful small bowel and multi-visceral transplants, which Tom was also the first to accomplish.

In 1990, Tom developed angina and was forced to stop operating. After an emergency coronary artery bypass, he recovered completely but decided that he would never operate again. Instead, now freed of an all-consuming surgery schedule, he elected to turn his full attention and energy to research.

Later he was asked if he missed operating. He responded, "No, I was relieved to get sick and have an excuse to stop. I was too much emotionally ruined by the loss of people I came to love. I always felt if somebody died who could have lived it was a doomsday event for me, and the burden of memories got to be too heavy. Of course the retreat was that I went back into research. And that turned out to be good too."

Tom's assertion that research also might be good proved to be an understatement. His goal now was to discover the Holy Grail of transplantation—immunologic tolerance that would allow drug-free immunosuppression.

Tom's innovations with immunosuppression have allowed excellent short and midterm survival of allografts. Nevertheless, because of the toxicity of immunosuppressive drugs and late graft loss from chronic rejection, drug-free immunosuppression or tolerance remains the ultimate goal. Plans for introducing tolerance invariably start with review of the 1953 demonstration by Billingham, Brent, and Medawar that chimerism induced in neonatal mice by inoculating them with donor strain lymphoid cells allows acceptance of donor strain grafts. In animal models there has been continued exploration of this strategy for inducing tolerance. But in humans this approach has been disappointing. In addition, since many successful transplants were accomplished without inoculating the recipient with donor cells, it seemed that donor cell chimerism must be irrelevant. For 30 years no one had suggested that allograft recipients had been successful because they

harbored donor lymphoid cells. But it was Tom's hypothesis that they did.

In 1992 Tom decided to search for donor leukocyte chimerism in a group of his patients who had maintained successful kidney or liver grafts for up to three decades. Sensitive immunochemical and molecular assays were used to detect donor cells. When these cells could not be found in blood, Tom searched for them in biopsies of skin, lymph nodes, and other tissues. He eventually found that small numbers of donor cells were in fact present in all of the 30 patients studied. Because these recipients had never been inoculated with donor cells, the chimeric cells could only have reached them as passengers migrating from the donor organ. Many of the patients appeared to be tolerant since they were off all immunosuppression.

This finding was the basis of Tom's belief that chimerism is an important cause—not a consequence—of successful transplantation. His demonstration of micro-chimerism in these patients has been an important stimulus for re-exploration of this approach for allograft tolerance in many centers.

In recent years Tom occasionally professed an intent to slow down and devote time to his non-medical and scientific passions and interests, including Joy—his wife of 36 years—music, and his dogs, which he took with him everywhere, including his office. This never happened. Instead he continued to direct the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh and search for methods of inducing tolerance. He made only one concession to the aging process. He stopped traveling to meetings unless he had to speak or accept a prize. This rule did not apply to meetings of his favorite society, the APS. In his two decades of membership he never missed a meeting.

Tom was almost certainly the most widely honored surgeon of his time. He had 26 honorary degrees from U.S. and foreign universities and 20 honorary fellowships from surgical colleges of other countries. His more than 200 other awards included the highest ones of the American Surgical Association, the International Transplantation Society, and the American Philosophical Society. Also the President's National Medal of Science, the Lasker Award, and the only surgeon membership in the National Academy of Sciences.

Until the end of his life Tom remained haunted by memories of tragic outcomes in his early transplant experience. But he had every reason to be proud of the changes he had brought about in the field. A fitting close to this incomplete summary of Tom's contributions to transplantation might be his own comments on the progress made in his time and its impact on the field of medicine.

Tom said:

> What looked like a hopeless dream, a fantasy has become a regular and reliable service, so good that the only limit is that there aren't enough donor organs. Within one or two generations it transformed the philosophy that guides medicine. Until the last 40 or 50 years if you had something like end stage heart or kidney or liver disease there was nothing you could do except try to squeeze out the last day of life sustaining function and that's all she wrote. Then all of a sudden, turn to the next chapter and you can replace the whole engine, not just a spark plug or two. So it's not hard to see why it changed the philosophy by which medicine is practiced.

Tom Starzl's influence has been multiplied by the accomplishments of the hundreds of surgeons who traveled to Colorado and Pittsburgh to learn from him. His disciples and subsequent generations trained by them continue to lead the transplant programs of the world.

Tom Starzl, the consummate surgeon scientist of our time, will be greatly missed by his trainees, his colleagues, his family, and his many friends at the APS. He is survived by his wife Joy, his son Timothy, and his grandson Ravi. He was predeceased by his daughter Rebecca and his son Thomas.

Elected 1999

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Author's Note

This biographical memoir is based on the paper "Tom Starzl and the Evolution of Transplantation" read by the author at the Autumn 2017 Meeting of the American Philosophical Society on 9 November 2017.