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# THOMAS STARZL, THE PIONEER OF THE LIVER TRANSPLANT. A HISTORICAL REVIEW

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## **INTRODUCTION**

Organ transplant is a fascinating field of modern medicine, and evolved in last one hundred years from preclinical and experimental studies to current clinical application. Organ transplant is not a new idea, but for many years it was limited to the homo- and heterografts of the skin. Transplantation as science was born in the beginning of the XXth century with early observations on the graft tolerance. A lot of efforts were done to solve technique, immunological and ethical issues. Many famous scientists contributed to our understanding and knowledge of organ transplant, like Schöne, Murphy, Carrel, Loeb, and many others, most of them almost

thought to be the father of modern organ transplant.

## **A (VERY) SHORT BIOGRAPHY**

Thomas Earl Starzl was born in LeMars, Iowa, on March 11, 1926. As a teenager he wanted to be a priest, but he moved to medical studies after the death of his mother by breast cancer in 1947. He studied at the Westminster College in Fulton, Missouri, and graduated with the degree of Bachelor of Science in biology. Then he attended Northwestern University Medical School in Chicago, and in 1950 he received a Master of Science degree in anatomy. Two years later he earned a PhD in neurophysiology and an MD with distinction



**Figure 1.**

Thomas Earl Starzl (1926-2017). The surgeon and the statue to remember the first liver transplant as it is today in Pittsburgh campus.

forgotten (Barker and Markmann, 2013).

Thousands of kidneys, heart, liver, lung transplants are performed in the world every year. Along the last decades, the life of hundreds of thousands of patients was saved with this procedure. Only in United States, more than 150.000 patients received a successful liver transplant in the last five decades. In this short review, we summarize particularly the research activity of Thomas Starzl, who performed the first liver transplant and it is

(Starzl, 1992). He wrote an important paper describing a technique to record the electrical responses of deep brain structures to sensory stimuli, which was cited almost 400 times by January 2019. After obtaining his medical degree, he was trained in surgery at Johns Hopkins Hospital and Jackson Memorial Hospital, and at both places, he conducted experimental studies with particular interest for the liver pathology. He moved in 1962 to the University of Colorado in Denver for almost two decades, and then to the University of Pittsburgh

in 1981. He retired in 1991 from the clinical activities, but remained active as professor till the end of his life. One building of the University of Pittsburgh was named Thomas Starzl Tower to celebrate his 80th anniversary. More than 25 Universities worldwide honoured him, and he also received more than 200 awards from important medical and non-medical institutions. He passed away at the age of 90, on March 4, 2017, at his home in Pittsburgh.

## **SCIENTIFIC CONTRIBUTION**

Thomas Starzl is a globally recognized pioneer in science and medicine, and he is best known as the first doctor which performed a successful liver transplant. On the other hand, it is believed that the success of the surgical procedure would have to wait for a while, in the absence of research works did before in both experimental and clinical conditions by the same person.

Everything starts from the heart: first steps in research. After the first success in research with a paper published in the Journal of Neurophysiology in 1951, he moved in the field of cardiology. This happened during his training in surgery at Johns Hopkins, and it was an 18 months full-time study in dogs of complete heart block, a frequent complication of the first human open-heart operations. The experiments involved creation of a canine model of heart block and treatment of its adverse consequences with repetitive low voltage ventricular stimulation (the first epicardial pacemaking) (Starzl, 2013). The procedure has been developed to treat the condition in animal model and eventually in patients.

Contribution of Thomas Starzl to the development of an efficient immunosuppressive protocol. The story started in 1963 in Washington, in a small conference where it was shown the short survival (months) of patients with kidney transplant. Kidney transplant was the only type of transplant performed at that time, and irradiation was used to prevent rejection of the graft. Unfortunately, it didn't work, and it was suggested that immunosuppression could have better results. During the conference, the unknown at that time Thomas Starzl presented an original immunosuppressive protocol that allow survival of the kidney graft more than 1 year in more than 70% of the cases. The innovation proposed by Starzl was the addition of prednisone to azathioprine, and after a while the doses could be diminished without inducing rejection of the graft (Starzl et al, 1963). Based on this innovation, the protocol was adopted in the United States and the number of patients with kidney transplant jumped immediately to over 50 per year. "Starzl immunosuppression cocktail" remained the standard protocol worldwide for almost 20 years (Brent, 1997; Barker and Markmann, 2013). Starzl developed this protocol based on his experimental studies in dogs (Starzl et al, 1961), and results he has shown in human patients made him from an unknown a famous specialist

in kidney transplantation.

How can be used anti-lymphocyte serum to the patients? The anti-lymphocyte serum was originally purposed by Ilya Metchnikoff in 1899, in order to mitigate the cellular immunity. More than fifty years later Michel Woodruff reported that anti-lymphocyte serum prolonged the skin graft survival in a rodent experimental model (Woodruff and Anderson 1963). The first application of the anti-lymphocyte serum in humans was done by Starzl in kidney allografts, and it was also used in the first human liver transplant in 1967 (Starzl et al, 1967a; Starzl et al, 1967b). It was a helpful opportunity, waiting for another immunosuppressive, namely cyclosporine.

Looking for an "ideal" immunosuppressive drug: cyclosporine. The drug that significantly changed the outcome of patients receiving organ transplant was cyclosporine that substantially improved results in kidney transplant (Barker and Markmann, 2013). Cyclosporine has been reported as a powerful immunosuppressive by Borel (Borel et al, 1976). Cyclosporine has been administrated as a single immunosuppressive agent in patients with kidney transplant, but immediate results were disappointing. Again, like in the case of azathioprine, Starzl added prednisone to the new drug and significantly improved the outcomes of patients with kidney transplant (Starzl et al, 1980). For almost a decade the protocol based on Cyclosporine and prednisone developed by Starzl was thought to be the standard procedure in immunosuppression in patients with organ transplant. It was in 1989 when Starzl and co-workers reported that rejection of the liver transplant can be reversed by Tacrolimus (Starzl et al, 1989), thus opening a new field in the immunosuppressive therapy. Based on this modern protocol of immunosuppression the kidney graft survival exceeds 1 year in more than 90% of the cases.

Do we have well preserved organs from the donor? It was early 1900's when Charles Guthrie introduced cooling to protect the graft before transplantation. Originally, Starzl used total body hypothermia to protect donor organs, but later on he infused cold solution into the portal vein to protect donor livers (Marchioro et al, 1963). This procedure became a routine in kidney transplant (Collins et al, 1969). The method proposed by Starzl and co-workers was helpful to preserve organs for transplantation for about two to three days.

The liver transplant: the man behind the legend. Starzl performed the world's first liver transplant in 1963 and the first successful liver transplant in 1967, both during his stay in Denver, at the University of Colorado. Originally, experimental studies were done in dogs, and results were used to design a protocol with potential

evidences of rejection during autopsy, but infections at multiple sites and pulmonary embolism. There were necessary other four years of study to build a successful protocol, as it happened in 1967. Improvements in organ preservation and immunosuppression strongly contributed to the success. Based on the data coming from the US and Europe, Everett Koop organized a conference on liver transplantation under the strong encouragement of President Ronald Regan, and thus, liver transplant became a clinical service in 1983. The papers published by Starzl about the liver transplantation are between the most cited in the clinical research and for sure, the most cited by works on liver transplant. The clinical thinking, steps and methods that finally led to the liver transplant in humans are excellently described by Starzl himself in the famous book, *The Puzzle People*. This is an ideal example on how to conduct a research, and how to move from the experiment to clinical application. Starzl wrote in 2013 about the patient (a young girl with biliary atresia) with longest surviving liver transplant: 42.7 years at that time.

What is chimerism and why does it occur? A major focus of Thomas Starzl research was the transplant tolerance and chimerism—the existence of cells from both the donor and recipient. His work in this area offered significant contributions to the understanding of transplant immunology, particularly with respect to how and why organs are accepted ([www.pitt.edu/news.starzl](http://www.pitt.edu/news.starzl)).

The story of Stormie Jones and the first synchronous heart-liver transplant. Stormie Jones was a young girl born in 1977 with a severe congenital hypercholesterolemia. Virtually, her liver was unable to process cholesterol and to remove the LDL-cholesterol from her blood. The high levels of cholesterol determined severe lesion of the heart, and she suffered two heart attacks till the age of six (Wikipedia, 2020). She was the first patient in the world receiving a simultaneous successful heart-liver transplant performed by a team directed by Starzl in Pittsburgh. The liver transplant worked well and reduced the blood cholesterol to normal values (Starzl et al, 1984). Unfortunately, Stormie died in late 1990, because of the rejection of the heart transplant she received six years before. The synchronous transplant prolonged the life of the patient with six years. The history of medicine retains Stormie as the first recipient of a simultaneous heart-liver transplant, and on the other hand, Thomas Starzl as leader of the team that performed it.

During the full career, Thomas Starzl published an impressive number of articles (1792 recorded in Pubmed, he authored or co-authored more than 2.200 scientific articles, four books, and 300 book chapters) sharing with all of us new findings, techniques, and protocols. The importance of his work is supported by the number of citations (more than 10.000 time only on the first page of Google Academic). As expected, he is the most cited author in the field of liver transplant and clinical medicine. Thomas Starzl was very active, very curious, and he permanently had new

ideas particularly in transplant pathology till last days of his life. His last article, „Augmenter of liver regeneration: a fundamental life protein” has been published in *Hepatology* in 2017, some months after he passed away (Nalesnik et al, 2017).

## **STARZL'S LEGACY**

We have a lot of things to learn from the life and medical career of Thomas Starzl. In the beginning of his career he was randomly invited in a meeting in 1963, and after no more than two decades he became a legend in organ transplantation. Starzl was a surgeon, immunologist, an expert in both experimental and clinical medicine. The story of human organ transplantation did not come to an end. Many questions are still waiting for an answer, many patients are on the waiting list to receive an appropriate organ. Many doctors are looking for new drugs and protocols, able to maintain the viability of the graft for decades. Today, there is a Thomas Starzl Institute for transplantation and a statue in the Campus of Pittsburgh University. But behind all those it is the man that show to the world that many patients with terminal liver disease have a chance. Based on the experimental, clinical, statistical, and archival research, his influence will continue to grow into the future.

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