

## A conversation with Thomas Starzl

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### Conversations with Giants in Medicine

Today in the United States, more than 6,000 people a year receive a liver transplant, and since liver transplants have begun, over 200,000 patients have received this therapy. They survive today due to the efforts of a legendary scientist and surgeon: Thomas Starzl (Figure 1) of the University of Pittsburgh Medical Center. He performed the first successful liver transplant in 1967 and refined the use of immunosuppressive drugs such that patients could tolerate their grafts — some for decades. With Starzl's efforts over the last 50 years, thousands of patients with end-stage liver disease have been able to live long and active lives. The full interview can be seen on the JCI website, <http://www.jci.org/kiosk/cgm>.  
JCI: What was your path to medical school? Starzl: I got to medical school via the Navy. I went from high school into the Navy for about a year and a half. And after discharge in October 1945, armed with the GI Bill, I was launched in what was a direction that had become increasingly clear — namely, medical school. I was interested in medicine, as my mother had been a nurse and I thought very highly of her. Because she had a high regard for doctors, I wanted to be one, probably for that simple reason. So in 1947, I was off to medical school [...]

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*JCI:* What was your path to medical school?

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So in 1947, I was off to medical school at Northwestern. After the first two years, I had developed a great interest in neuroscience and then I dropped out for almost a year and a half to do pure research in neuroscience, which resulted in a PhD. After dropping out again a year later, I finally went back, got my medical degree, and went to Johns Hopkins for residency. There, I went into another side alley — cardiac physiology. After we had encountered complete heart block in some of the early open-heart operations, we needed to develop some way to deal with that complication. I developed a model of complete heart block in dogs, studied the physiology, figured out how to do pacemaking, and solved the problem. And during the rest of my residency, I developed an interest in metabolism; and in the course of pursuing that interest, developed models of transplantation that involved either the liver alone or the liver with other abdominal viscera.

At the time, immunosuppression did not exist, so the models were in unmodified animals that received no immunosuppression. The real opportunity here was for the study

of the rejection patterns of liver allografts. One of the interesting observations that was made in those untreated animals was an occasional recipient who rejected, became jaundiced, and then spontaneously recovered. In those animals, the pathology was remarkably changed after the chemical reversal of rejection, in that the invading cells that were characteristic of rejection just disappeared. Everything that we could see from that point on looked like remodeling, regeneration, and repair. So even before the availability of immunosuppression, I had a very clear idea that rejection was potentially spontaneously reversible. By 1959, I also developed a model of multi-visceral transplantation in which the liver was transplanted with the intestine, pancreas, and the rest of the abdominal viscera. In those experiments the rejection of these extra organs was much less than if the organs had been transplanted alone. This background of behavior of grafts, and specifically liver grafts or those organs that were transplanted with the liver, provided a platform upon which all of the later observations with immunosuppression could be built on.

*JCI:* In one of the interviews you have given in the past, you mentioned that there was a moment when you were facing so much uncertainty about the nature of your research that it was hard to get funding. At the time you were finishing your clinical training, during a trip you had to spend the night in a movie theater and on a park bench, and on one occasion you had to smuggle a lab rabbit out of your lab at Northwestern in order to feed a visiting professor. How did you weather that period of uncertainty?

Starzl: Those are true stories. I don't know that I gave it the kind of deep thought that you're implying I should have, but somehow I thought that everything was going to turn out all right. I was a missile searching for a trajectory; I was bursting with energy. I really wanted to do something that wasn't conventional, wasn't going to be bread and butter surgery as a means of making money, but I wanted to do something important that would have a life of its own, that would endure. But what to do? I had come to be regarded as a dilettante, having gone through a PhD in neuroscience, and then a PhD equivalent

in working out the heart block problem. And here I was wandering around not pursuing either field. I just didn't know what to do with myself. I was also getting pressure from my father who was getting sick of sending me money. I was getting pressure from my first wife's family, who had means, but they didn't like the idea of providing a dole, and I was even more uncomfortable in accepting that kind of help.

So the problem was really what field I should be working in. I had skills in cardiovascular surgery, in general surgery, and other surgical skills that I acquired over an educational period that lasted from the time that I got out of the Navy. I had perpetual student syndrome or a dilettante syndrome. I like to think of myself as a gifted dilettante, but being a dilettante in and of itself is not a good idea.

I found a trajectory at Northwestern with the transplant studies because I spent about two years of full-time duty, working all day every day, on that project. I settled the financial problem by developing a practice of tertiary surgery at a neighborhood hospital called Lutheran Deaconess Hospital. I had a special relationship with them that allowed me to operate before the rest of the schedule began at the hospital. But that necessitated being there at five in the morning doing the cases so I could show up at the laboratory at nine o'clock, and this went on for a while. I was so tired by this schedule that I didn't think that I would be able to live beyond the age 40 if I kept this up. So it was at that point that an opportunity came to go to Colorado and I took it.

*JCI:* It was there that you started testing a cocktail of immunosuppressive drugs and steroids together on your kidney transplant patients?

Starzl: Almost. The first thing that was done within the first few months of 1962 was to obtain a supply of the drug from Upjohn. I obtained a supply of azathioprine (Imuran) probably a year after Roy Calne in England had tested it. I then made some observations that were completely missed by the people that had the first crack of the drug, including Calne. What they had done was to use the Imuran from the time of operation and then they put it together with the variety of other drugs, including other cytotoxic drugs; but also they had tested it



**Figure 1**

Ushma Neill interviews Thomas Starzl in New York City on September 21, 2012, after he received his Lasker-DeBakey Clinical Medical Research Award. Image credit: Semyon Maltsev.

with prednisone. They began these secondary drugs at the same time as they started Imuran in their dogs. The prednisone actually degraded the results, made them worse. This led to an anti-steroid point of view by most scientists, but I had always treated with Imuran alone and then only when rejection developed in the dogs did I add the steroids. I found out that rejection was always reversible or essentially 95% of the time was reversible, and that sometimes, you could then stop the steroids. In our experiments, because we had limited kennels, we always stopped our drugs completely at 100 days and, to our amazement, most of the liver recipients did not reject.

The other thing that we showed is that if you pretreated the animals with Imuran for a couple of weeks before, and then continued afterwards, the results were about double in survival of what they were if you just started on the day of operation. The conditions with which we tested Imuran were quite different than the other centers, and it was that set of observations that prompted going forward with the kidney program. Why kidney when my first interest was the liver? I realized that if we pro-

ceeded with the liver without making the kidney work, that it would be considered borderline criminal.

The first objective then was to make kidneys work and use that as a porthole through which you could mount a liver program, which succeeded at least at a proof of critical principle level in 1967. So, between 1967 and the time I moved to Pittsburgh, or until the time that cyclosporine became available (1967–1979), there was a long period of time in which there were multiple successes — but the survival rate was only 50%.

Losing half the liver recipients during the first year was a very tough pill to keep swallowing. Never during those dozen years could I see any way that I could improve things. When Roy came up with cyclosporine in a report in 1979, I was all over the company to get a supply of the drug to try it. I did the first 12 successful liver cases with cyclosporine while I was still in Colorado, and about 60 kidney cases.

*JCI:* Do you have any memories of particular patients during that period that shaped the way that you approached your research and surgical techniques?

Starzl: I remember all of my patients as if they were family members. The proof of principle cases over the period between 1967 and 1980 were very precious people. I could never get them off my mind.

*JCI:* Given that your father was a writer and the newspaperman, it is not shocking that you also are a very prolific writer with several books, important textbooks, and over 1,800 scientific articles. Do you have a special affinity for the written word?

Starzl: It has always been easiest for me to transform thoughts on to paper. Some people have a great and wonderful fluency in speaking, and I always feel clumsy about that. When I talk to you, I am automatically envisioning written sentences and so it slows up my talk. So the written word was an escape from that. Also it was a filter, because if you write things down before you expose them, you have chance to do all kinds of corrections before they ever become visible to anyone else; and I like that. I like the care that you put in the written word. I don't like a situation where you write something down and immediately transmit it — like with e-mail.

*JCI:* In September 2012, together with Sir Roy Calne, you were awarded the Lasker-DeBakey Clinical Medical Research Award recognizing the great strides that both of you took towards successful liver transplantation.

Starzl: It was tremendously gratifying. It came really unusually late in life for us. Roy is 84, and I am coming up on 87. So there is some advantage to having this occur so late because it always kept the fire burning hotter than it would have if something like this had happened 20 years ago.

*JCI:* Did you ever consider a different career other than being a doctor and surgeon?

Starzl: No, I don't think I ever did. By the time I was 10 or 12 years old I was going to the hospital, the only one in Le Mars, Iowa, and watching a surgeon named Downing. He was a general practitioner who was also a quite skillful surgeon doing major operations, radical mastectomies, and other procedures. He was quite surprised when I went to his office and asked him if I could come up and watch his operations and he allowed me to do that, taking pains to be able to cart a fainted body out of the room, which happily didn't occur. So I don't believe I ever considered any other pathway from the time I was a sub-teenager onward.

**Ushma S. Neill**