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Understanding translational research: A play in four acts

Eric A. Rose

Population Science and Health Policy, Surgery, Cardiovascular Surgery, and Medicine, Mount Sinai School of Medicine, New York, NY, United States

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ABSTRACT

Translational research (TR) bridges discovery to clinical delivery. All TR also requires the development of an intervention. Classical 'bench to bedside' TR is responsible for many important advances, but cannot account for many others, which begin with clinical observations. My personal involvement in TR has ranged from exploration of long-term mechanical circulatory support devices to amelioration of the progression of Alzheimer's disease to the pharmacologic cure of smallpox. This experience suggests that most TR is opportunistic and inefficient. A strategic approach to TR based on a better understanding of the processes it entails could enhance progress in TR despite its increasing complexity.

Good morning. It's really a pleasure to be here at this meeting. I've gotten a chance to meet many, many former residents, old friends, colleagues at Columbia University, and others that I have met through the years that have generated great friendships and wonderful camaraderie.

I suspect it was Charlie Stolar who began the conspiracy to invite me to deliver this lecture. When Tom Krummel contacted me, I wasn't sure he was speaking with the right person but, after a few brief minutes, I think we connected in a way that generated the talk that I'm about to give.

If this were a play, it would have four acts and be titled "Observational versus Interventional Biology." It is not going to be a Broadway hit, but the context of my remarks starts with understanding this difference. When I was a resident, after two years I was lucky enough to be asked to do an NIH-supported resident fellowship, and I chose to work in a surgical metabolism laboratory where I was assigned to a project to measure levels of all 21 amino acids in soleus muscle in intensive care unit patients. I did this for two to three months. I diligently learned how to do the measurements and, not surprisingly, for some of them the levels went up, some of them went down, some of them stayed the same. I started wondering, what am I going to do with this? What's the meaning of it all?

I really could not come up with an answer. I went to my program director, Dr. Thomas King, to lament this problem and he fortunately was receptive enough to transfer me into a laboratory in cardiac surgery looking at ventricular assist devices, a space that I have been in now for more than 35 years. But the difference here is observational versus interventional. Observational biologists want to understand the laws of God and nature and describe phenomena that over time perhaps we would understand, but not necessarily look for anything more than that. I think there is enormous merit in doing that, but for people like you and me, this being a surgical organization, it's fair to say that our bent is more to interfere with the laws of God and nature rather than just understand them. Fortunately, I was able to redirect my efforts at that time and the following four acts follow from that.

1. Act 1: adventures in mechanical circulatory support

Dr. Keith Reemtsma was good enough to hire me out of a residency in cardiothoracic surgery in 1982 and assigned me to lead a heart transplant program that had stopped functioning for a period of time because of poor results. It was a time when Massachusetts General Hospital had just stopped doing heart transplantation. The *New York Times* had editorialized that it was a horrible thing to do and a waste of time and money, and it was probably the single most important opportunity of my life. We grew the Columbia heart transplant program to be one of the largest in the world but there were a few things that became disappointingly obvious doing a hundred or more heart transplants per year: the impact of the procedure was high for the individual patient but for the universe of patients with heart failure the operation was epidemiologically trivial.

For Keith it meant investigating cross-species transplantation and he and I worked together on that for several years [1]. But with the onset of institutional Animal Care and Use Committees pursuing xenotransplantations in humans using chimpanzees as donors became a dead-end. So I got interested in mechanical circulatory support devices,

E-mail address: erose@MAFGRP.COM.

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which have since had a remarkable run. The mechanical alternatives available were and are left ventricular assist devices and total artificial hearts, and without question the former have dominated this field for decades [2]. The devices that I investigated initially in the late 1980s and early 1990s would now unquestionably be viewed as primitive. They were enormous, the size of a compact disk player. The pulsatile pumping component was implanted in the abdomen and attached to the apex of the left ventricle through an incision in the diaphragm [3]. A lot of surgery. Big bulky multi-kilogram devices that connected across the skin to control consoles the size of a refrigerator [4]. In the late 1980s a so-called "wearable" configuration was engineered so that the control unit was reduced to a size that could hang on a belt like a large beeper [5]. Patients were outfitted with a couple of batteries worn in a holster as well to power the implanted electric motor integral to the device.

We did the most important work in this field not in animals, not in dogs or calves. We did it in people in the scenario called "bridging" to transplant [6]. Namely, we had patients who had terminally failing hearts who were not going to make it to the point of receiving a donor organ in time to survive into whom you could implant a device in the hope that that donor organ at some point would show up. We learned an enormous amount in that clinical theater, but if the only use of these devices was to be a bridge to transplant, all we would be doing is changing the identity of the recipients. There is no net epidemiologic impact unless you actually use these devices long term *without* transplantation as the ultimate goal.

But we learned a lot from bridging to transplantation. We learned that we could discharge patients from the hospital, an enormous accomplishment in the early 1990s. We learned that there was plenty of device related morbidity but it was finite and possibly acceptable compared to the morbidity of end-stage heart disease. We also learned that at least certain types of device failure, and there were plenty of types of device failure, did not require reoperation. Probably most importantly we learned about quality of life that patients had with these devices, which was hardly normal. The typical patients carried a 2-kilo device in the abdomen connected across the skin to a wearable controller. They wore two batteries all the time that alarmed frequently: hardly an easy way to live, but compared to being short of breath at rest it was preferable. It allowed these patients to enjoy a lot of things that they otherwise could not.

Then came the critical question: can these devices be used long-term, what we termed a "destination," therapy rather than a bridge to transplantation? This seems like a simple question, but the common view at that point was that the Food and Drug Administration (FDA) would never allow this. There was the not unfounded view that devices were too complicated and unsafe [7]. The device manufacturers were resistant to doing randomized prospective trials to rigorously test safety and efficacy, and physicians were of two camps – assist devices were either great or they defied the laws of God and nature and implantation was unethical.

Not surprisingly, it took a decade to put together a trial called the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure, REMATCH in order to resolve the controversy [3]. The trial was NIH supported, but it took three applications to get this funded. (That process in itself could be an interesting play.)

First, we had to get a device manufacturer involved. The leading company at that time in the field refused to participate in the trial, and the device that we used had certain advantages but certain disadvantages, one of which was durability. The hypothesis behind the trial was, first and foremost, that device implantation would reduce mortality. Specifically, we thought that a one-third reduction in mortality over two years would be meaningful in light of the fact that pharmaceutical trials typically showed a 20% reduction in mortality over that interval.

But equally important was patient quality of life. If it was worse on devices, then arguably all we were doing was prolonging death, so it was equally important that we acquired good data on quality of life in order to validate the technology [8].

The essentials of this study were multiple. It required multiple academic institutions and clinical groups, the NIH and a device company that entered into a formal cooperative agreement that it took lawyers more than a year to negotiate. There were 20 centers involved. It's hard if not impossible to do a trial like this with blinding and this was a major early criticism. There were some who even thought that the way to do the trial was to implant devices in everybody and only turn them on in the active group. Needless to say we declined to use this approach and IRBs would have kept us from it. We also looked at issues of cost and cost effectiveness because we thought this set of data was going to be used by Medicare in order to set reimbursement levels and we wanted that to happen as part of this trial. We estimated it would take about 140 patients in order to have a 90% power to document the survival benefit that we hypothesized. We reported this data in the *New England Journal of Medicine* and at the American Heart Association in November, 2001, [3] a time when there was a lot of news about a lot of other things other than end-stage heart disease and mechanical circulatory assistance, but the trial did have a number of important implications and outcomes besides its positivity with regard to survival and quality of life. Obviously we had first proof of survival benefit over an extended period and this in many respects is what enabled the industry of ventricular assist devices to become commercially viable. On a regulatory level this was a phase 3 pivotal trial and it led to approval of the device we investigated and now multiple generations of successor devices that have all been evaluated and randomized in noninferiority trials [9]. There is no longer the need for a non-device control group that you need to do in order to evaluate a long-term ventricular assist device in end stage heart failure patients. In terms of health policy, the cost analysis guided a coverage decision from Medicare which came within about a year and a half of the original trial report. Importantly, the relatively poor device outcomes, and these included seven major adverse events per patient year in the survivors, provided a benchmark that allowed comparisons of second and third-generation devices that are now under evaluation. To give you a sense of what a third-generation VAD looks like, this is a Circulite VAD [10] (Fig. 1). This is a company whose board I chaired for a couple of years. It was sold to HeartWare recently. You can see this is about the size of an AA battery. We now have implantation technology that allows the inflow portion of this device to be inserted through the superior vena cava across the atrial septum, which means that you don't have to do a thoracotomy or a sternotomy, to implant it. We've done animal experiments using that implantation technique. The pump itself has been in approximately 75 patients, but the percutaneous implantation I believe will happen first in man probably in the next year or two. It's very exciting, and it's come a long way from the massive early pumps.

The purpose of my talk today is to talk to you about translational research generally, and there is a lot that I summarized in just a few minutes on mechanical circulatory support. But the work took more than 20 years. REMATCH alone took more than a decade to accomplish, and during that time there was plenty to think about.

What's to be learned from an experience like this? Probably first and foremost is that the current linkages between academia, industry and government are at best opportunistic. They don't happen on a strategic basis and many of these linkages are suspect from the vantage point of conflict of interest. I actually neglected to put up a conflict of interest slide. I think most of you see them in every talk and I get the sense that we have all desensitized to them. I've even heard somebody once make the comment that if you don't see your company up on my conflict slide, please see me after the presentation. This is the world in which we live, that any kind of interaction is subject to scrutiny and subject to suspicion. At the same time as there are these perceived conflicts of interest, there is unprecedented opportunity for collaboration, especially at early stages when these technologies and approaches are so fragile. I think intelligent policy making requires understanding the process of translational research and participating in translational research requires a good understanding of the process as well. That's what I hope to give you in the next three acts of this play.